



## Short communication

## Mortality and causes of death among users of methadone maintenance treatment in Israel, 1999–2008

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## ABSTRACT

**Objectives:** To determine all-cause and specific-causes mortality, in the years 1999–2008, among opioid-dependent users treated at methadone maintenance treatment (MMT) clinics in Israel and to compare the obtained results with data from relevant studies worldwide.

**Method:** The records of patients treated at MMT units were linked to the nationwide database of causes of death. Information about the Israeli general population from the Central Bureau of Statistics was used for comparison to match sex and age to the cohort under study. Crude mortality rates (CMRs) per 100 persons per year (PY) and standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) were calculated.

**Results:** The overall CMR for MMT users was 1.49/100 PY (CI 1.40–1.59) and was not associated with gender, age at entering MMT, ethnicity, and immigrant status. The leading causes of mortality were sudden/undefined death (0.31/100 PY, CI 0.26–0.35), overdose (0.22/100 PY, CI 0.17–0.27), and cancer (0.15/100 PY, CI 0.12–0.18). The MMT users were 12.2 times more likely to die from all causes than people from the general population. Overall, our estimates were comparable with the figures pooled from relevant studies.

**Conclusions:** The results suggest that the excess mortality of MMT users is associated with an increased morbidity, which alone or in combination with service-related risks, lead to worse outcomes.

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## 1. Introduction

Opioid dependence is a chronic medical disorder characterized by an individual's inability to stop using opioids, despite the significant social and health harm caused by that misuse (American Psychiatric Association, 1994). Apart from increased criminal behavior with subsequent imprisonment, typical problems of these people are opioid overdose and increased morbidity associated with intravenous injecting of the drug, such as immunosuppressive/immunoproliferative infections: human immunodeficiency virus (HIV; Shiels et al., 2010), hepatitis B virus and hepatitis C virus (HBV/HCV; Amin et al., 2006), and human papilloma virus (HPV; Walboomers et al., 1999). As a result, mortality rates among opioid-dependent people are higher than for the general population, with some differences between countries and ethnic-religious groups (Degenhardt et al., 2011). The majority of deaths

among opioid-dependent people occur from accidental poisonings (Sanchez-Carbonell and Seus, 2000), but also deaths from natural causes, such as cancer (Grinshpoon et al., 2011), cardiovascular disorders (Darke et al., 2006), and respiratory diseases (Albion et al., 2010) are higher than in the general population.

A recent meta-analysis of 58 prospective cohort studies reported standardized mortality ratios (SMRs) from opioid-dependent samples (Degenhardt et al., 2011) and computed the pooled SMR as 14.66, with overdose as the most common cause of death. A prospective observational study in UK reported that opiate substitution treatment with methadone or buprenorphine in primary care had a greater than 85% chance of reducing overall mortality among opiate users if the average duration of the treatment approaches or exceeds 12 months, despite the increased mortality risk at the start and immediately after stopping the treatment program (Cornish et al., 2010).

Only one prospective study was conducted in Israel that examined mortality risk and causes of death among opioid users in a methadone maintenance treatment (MMT) center (Peles et al., 2010). This study found that of 613 patients followed-up over 15 years, 94 died (15.3%); cancer was the primary cause of death for

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**Table 1**  
Demographic characteristics, number of deaths, and crude mortality rates (CMRs) of MMT users.

Characteristic	N	%	Average age <sup>a</sup>	Deaths N	CMR <sup>b</sup>	95% CI <sup>c</sup>	
						Lower	Upper
Total	9818	100	40.9	960	1.49	1.40	1.59
Gender							
Male	8452	86.1	41.4	847	1.53	1.42	1.63
Female	1366	13.9	37.9	113	1.29	1.05	1.53
Population group							
Jews and others <sup>d</sup>	1983	20.2	40.8	787	1.54	1.43	1.65
Israeli-Arabs	7835	79.8	41.6	173	1.31	1.12	1.51
Immigration status							
Immigrant from 1991	2139	21.8	34.6	195	1.59	1.37	1.81
Native-born or immigrant before 1990	7679	78.2	42.4	765	1.47	1.37	1.58

<sup>a</sup> Average age adjusted for follow up time. Date and age of beginning treatment missing for 986 patients.

<sup>b</sup> CMR = number of deaths per 100 persons per year of follow-up.

<sup>c</sup> 95% CI = confidence interval.

<sup>d</sup> Others = Non-Arab Christians and those not classified by religion in the Ministry of Interior.

those who remained in treatment, while overdose for those who left MMT. The study also noted that mortality was associated with pre-treatment severity of opioid dependence and comorbidities. Because the single-center study had small sample-size and person-years of observation, its findings are inconclusive at country-level. Therefore, a study using data from all MMT centers in Israel would provide more accurate information.

This study aimed (1) to determine all-cause mortality and specific causes of death of MMT users in Israel between 1999 and 2008, and (2) to examine how mortality rates vary by sex, age, ethnicity, and immigrant status.

## 2. Method

### 2.1. Data sources and study sample

The number of MMT clinics in Israel comprises 13. Records of patients who were ever treated were collected from the different clinics. The identity of patients was verified by comparison with the national population registry, which enabled verification and completion of sociodemographics (gender, age, ethnicity, and immigrant status), and removal of duplicate records, since many patients were treated at more than one facility. For 2.5% of the records sent to the national population registry, a match was not found, and they therefore did not enter the study. The study period for mortality follow-up was from 1999, when patient data was more complete and reliable.

The sample consisted of patients who had ever been treated or were currently in treatment in MMT clinics till 2008. Total person years of follow-up were calculated from the beginning of study (1999) or first treatment (if after the beginning of 1999) till death or end of the study (2008) or age 65. Maximum period of follow up was thus 10 years.

The nationwide database of causes of death is under the responsibility of the Central Bureau of Statistics (CBS). Since 1998, causes of death were coded according to the International Classification of Diseases-Tenth Edition (ICD-10) (World Health Organization, 1993; see Goldberger et al., 2011).

Using deterministic record linkage design, the mortality records with causes of death for the years of our study, 1999–2008, were linked to the verified records of MMT users, via their unique 9-digit national identification number, to find those who died and their cause of death.

### 2.2. Study variables

The outcome variable was all-cause death (incidence of mortality). Crude mortality rates (CMRs) were calculated by age (grouped as: 18–35, 35–44, 45–54, and 55–64) gender, ethnic group and immigrant status. Death rates were calculated for all causes, all natural and all external causes, and largest subgroups for addicts, natural: cancer (C00–C97), heart diseases (I00–I09, I11, I13, and I20–I51), viral hepatitis (B17–B19), chronic lower respiratory diseases (J40–J47), chronic liver disease and cirrhosis (K73–K74 and K70), psychoactive substance abuse (F10–F19) and sudden/undefined cause of death (R96–R99); external: suicide (X60–X84 and Y870), homicide (X85–Y09 and Y871), accidental drug poisoning (X40–X44), drug poisoning of undetermined intent (Y10–Y19), and other accidents or other external causes (V01–X39, X45–X59, Y20–Y86, Y88–Y89, and Y872).

### 2.3. Data analysis

All data were linked and analyzed using SAS 9.2 (Cary, NC: SAS Institute Inc.). Expected number of total and cause-specific deaths was calculated as the sum of person years of treated subjects in each age group multiplied by the age specific rate in the general population of Israel. SMRs were calculated by dividing the number of observed deaths by the expected number of deaths. Calculation of 95% confidence intervals (CIs) of SMRs was based on the assumption that the observed number followed a Poisson distribution. Since the large majority of subjects were male, sex pooled SMR analyses were used.

## 3. Results

The sample consisted of 9,818 individuals (86.1% male and 79.8% Jewish), who had ever been treated or were currently in treatment in MMT clinics till 2008 (Table 1). The immigrants and females were younger than the non-immigrants and males, respectively. Their total person-years of follow-up were 64,225. The mean follow-up time was 6.54 years (SD = 3.31) and median follow-up time was 7.13 years. The majority of participants (82%) began treatment before age 45, and 21.8% were immigrants to Israel since 1991. Of those who died more than 60% were under treatment or within 6 months of the last treatment, and only 7.5% were more than 5 years from the end of last treatment in the MMT program.

### 3.1. Mortality by demographics

Table 1 also shows number of deaths and CMRs per 100 person-years with the respective 95% confidence intervals (CIs) by demographic characteristics. Over the 10-year follow-up period, there were 960 deaths. No significant differences were found between the CMR for different genders, ethnic groups or by immigrant status ( $p$  for chi-square test > 0.05).

### 3.2. Mortality by cause

Table 2 shows the numbers of observed and expected deaths, CMRs per 100 person-years, and SMRs with respective 95% confidence intervals (CIs) overall and by different causes of death. The overall CMR for the MMT cohort was 1.495 per 100 PY. In addition to deaths with an underlying cause directly related to drug abuse—from liver disease, viral hepatitis, drug dependence, and drug poisoning (accidental and undetermined intention), accounting for 30% of deaths, a further 20% of deaths were sudden/undefined deaths which could also be drug-related, and 9% were from suicide or homicide.

**Table 2**

Number of deaths, crude mortality rates (CMRs) per 100 person-years and standardized mortality ratios (SMRs) by causes of death.

Cause	Observed deaths	% of all deaths	CMR	95% CI		Expected deaths	SMR	95% CI	
				Lower	Upper			Lower	Upper
Natural	631	65.7	0.982	0.906	1.059	59.1	10.7	9.8	11.5
Cancer	96	10.0	0.149	0.120	0.179	24.5	3.9	3.1	4.7
Heart disease	46	4.8	0.072	0.051	0.092	7.5	6.1	4.3	7.9
Viral hepatitis	48	5.0	0.075	0.054	0.096	0.4	108.0	77.4	138.5
CLRD	23	2.4	0.036	0.021	0.050	0.9	25.3	15.0	35.7
Liver disease	21	2.2	0.033	0.019	0.047	0.9	23.0	13.1	32.8
Psychoactive substance abuse	74	7.7	0.115	0.089	0.141	0.9	84.0	64.9	103.2
Sudden/undefined	196	20.4	0.305	0.262	0.348	24.5	23.7	20.4	27.0
Other natural	127	13.2	0.198	0.163	0.232	15.7	8.1	6.7	9.5
External	318	33.1	0.495	0.441	0.550	1.8	16.5	14.6	18.3
Suicide	53	5.5	0.083	0.060	0.105	4.8	11.1	8.1	14.1
Homicide	34	3.5	0.053	0.035	0.071	2.3	14.6	9.7	19.5
Accidental drug poisoning	41	4.3	0.064	0.044	0.083	0.6	67.8	47.1	88.6
Undetermined drug poisoning	98	10.2	0.153	0.122	0.183	1.6	60.4	48.4	72.4
Other accidental/external deaths	92	9.6	0.143	0.114	0.173	10.0	9.2	7.3	11.1
Total <sup>a</sup>	960	100.0	1.495	1.400	1.589	78.7	12.2	11.4	13.0
Total drug overdose related <sup>b</sup>	213	22.2	0.332	0.376	0.287	3.1	68.5	59.3	77.7

<sup>a</sup> Includes cases with missing cause of death.<sup>b</sup> Total of psychoactive substance abuse and drug poisonings (accidental and with undetermined motive).

### 3.3. Comparison with the general population

Table 2 shows also that mortality was higher for all causes amongst MMT users compared to the general population, with SMR of 12.2 (95% CI 11.4–13.0) for all deaths, and even higher (16.5, 95% CI 14.6–18.3) for deaths from external causes. The highest SMR's as expected were for causes related to drug dependence. But other natural causes with deaths about 25 times higher for MMT users were chronic lower respiratory disease, liver disease, and sudden or undefined deaths. Suicide and homicide were also much higher, while deaths from cancer and heart disease, while also higher, had the lowest SMR's, 3.9 and 6.1, respectively. Results are not presented for HIV deaths, since there were only 15 cases amongst MMT users.

## 4. Discussion

### 4.1. Comparison with the general population

As expected, a significant proportion of mortality of those in MMT treatment was due to causes directly or indirectly connected with their drug usage. The SMR for viral hepatitis, in particular, associated with intravenous injecting of the drug, is very high, since it is rare among the general population, as, for example, was reported in a cohort study that prevalence of viral infections, HIV, HBV and HCV were significantly more common among injecting drug users compared to native Israelis (Loebstein et al., 2008). Other excess mortality from natural causes suggests either an increased morbidity (Lawrence et al., 2010) or a worse-case outcome, even if incidence is not increased. High risk behaviour of more tobacco and alcohol involvement than the general population was reported in case-control studies using convenience samples of heroin-dependent Jewish men (Neumark et al., 2002; Isralowitz et al., 2001).

A recent study in Israel (Grinshpoon et al., 2011) reported increased compared to the general population, cancer morbidity among MMT users, with higher age-standardized incidence ratio for lung, larynx and liver cancers among Jewish men and for cervix uteri cancer among Jewish women. Another possible explanation for the excess mortality of opioid users from natural causes is service-related risks, i.e., barriers for receiving appropriate and timely medical care and poor recognizing and treatment of physical conditions which they share in common with people suffering

from other mental disorders (Kisely et al., 2007; Haklai et al., in press).

Higher mortality from external causes of homicide, suicide, and accident suggests that opioid users are substantially exposed to risk-taking behaviors other than actually taking drugs, such as having unprotected sex, gambling, robbing, committing an act of aggression or violence. The reasons for these behaviors are complex, but the major motive for risk takers is gratification from the danger involved in these antisocial activities. Antisocial risk takers generally have a socially negative outlook and repeatedly engage in activities that society perceives as abnormal and leading to violence and self-destruction (Wilson et al., 2002).

### 4.2. International comparisons

Our overall CMR (1.50) was somewhat lower than the pooled CMR reported (Degenhardt et al., 2011) for 57 cohorts across the world (2.09), probably due to the limit of our follow up to age 65. The overall SMR in our study (12.20) also was lower than the pooled SMR (14.66). Cause specific mortality rates were also similar except for drug overdose, which was much lower. But if deaths coded as sudden or unknown cause of death, likely also to be due to drug overdose (CMR = 0.30/100 PY), are added to those from drug overdose (CMR = 0.33/100 PY), the total is almost identical to that of the pooled estimate (CMR = 0.65/100 PY). Amongst natural causes, the SMR for cancer was considerably higher in Israel.

### 4.3. Factors associated with mortality

The relatively increased risk of mortality for males was similar to the pooled results from 33 cohorts (Degenhardt et al., 2011) and probably reflects the younger age of females. We did not find significantly higher mortality among Israeli-Arabs or recent immigrants, although general death rates are considerably higher amongst Israeli-Arabs (Gal et al., 2012), and a recent epidemiological study found that mortality among former Soviet Union immigrants (who form the majority of recent immigrants) from external causes and cancer considerably exceeded that of the host country (Ott et al., 2009). The increased risk of mortality seems higher for Jews and Others than Israeli-Arabs. The younger average age of the new immigrant group might account for their relatively low rates.

#### 4.4. Strengths and limitations

The strengths of this study are: (1) the representative sample that covered all opioid users treated in all MMT centers in Israel from the beginning of the 1990s. (2) Coding causes of death were coded according to ICD-10, which helps eliminate inconsistencies in recording drug related deaths. (3) Calculation of all-cause and cause-specific CMRs and SMRs enabling future international comparisons.

Our study was limited since our data on dates of treatment episodes was not sufficiently exact to compute in and out of treatment rates, to confirm the finding of higher out of treatment mortality rates (Peles et al., 2010; Haklai et al., in press). Our follow-up period was also a maximum of 10 years, which did not enable study of treated patients of older ages—we limited the study to those aged fewer than 65 since so few were older.

#### 4.5. Conclusions

Our study shows much higher mortality rates amongst MMT users than the general population, similar to results found in other studies. The excess mortality from natural causes may be associated with increased morbidity, which alone or in combination with service-related risks, lead to worse-case outcomes.

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#### Contributors

All authors contributed to the analysis and interpretation of the data presented in this paper. All authors have read and approved the final manuscript.

#### Conflict of interest

None.

#### References

- Albion, C., Shkrum, M., Cairns, J., 2010. Contributing factors to methadone-related deaths in Ontario. *Am. J. Forensic Med. Pathol.* 31, 313–319.
- American Psychiatric Association, 1994. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*. APA, Washington, DC.
- Amin, J., Dore, G.J., O'Connell, D.L., Bartlett, M., Tracey, E., Kaldor, J.M., Law, M.G., 2006. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. *J. Hepatol.* 45, 197–203.
- Cornish, R., Macleod, J., Strang, J., Vickerman, P., Hickman, M., 2010. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *Br. Med. J.* 341, c5475.
- Darke, S., Kaye, S., Dufflou, J., 2006. Comparative cardiac pathology among deaths due to cocaine toxicity, opioid toxicity and non-drug-related causes. *Addiction* 101, 1771–1777.
- Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., McLaren, J., 2011. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction* 106, 32–51.
- Gal, G., Goldberger, N., Kabaha, A., Haklai, Z., Geraisy, N., Gross, R., Levav, I., 2012. Suicidal behavior among Muslim Arabs in Israel. *Soc. Psychiatry Psychiatr. Epidemiol.* 47, 11–17.
- Goldberger, N., Aburbeh, M., Haklai, Z., 2011. Leading Causes of Death in Israel 1999–2008. Ministry of Health, Available at <http://www.health.gov.il/pages/default.asp?maincat=2&catid=841&pageid=4433>. Accessed on 15/8/2011 (in Hebrew).
- Grinshpoon, A., Barchana, M., Lipshitz, I., Rosca, P., Weizman, A., Ponizovsky, A.M., 2011. Methadone maintenance and cancer risk: an Israeli case registry study. *Drug Alcohol Depend.* 119, 88–92.
- Haklai, Z., Goldberger, N., Stein, N., Pugachova I., Levav I., in press. The mortality risk among persons with psychiatric hospitalizations. *Isr. J. Psychiatry Relat. Sci.*
- Isralowitz, R., Reznik, A., Spear, S.E., Brecht, M.L., Rawson, R.A., 2001. Severity of heroin use in Israel: comparisons between native Israelis and former Soviet Union immigrants. *Addiction* 102, 630–637.
- Kisely, S., Smith, M., Lawrence, D., Cox, M., Campbell, L.A., Maaten, S., 2007. Inequitable access for mentally ill patients to some medically necessary procedures. *CMAJ* 176, 779–784.
- Lawrence, D., Kisely, S., Pais, J., 2010. The epidemiology of excess mortality in people with mental illness. *Can. J. Psychiatry* 55, 752–760.
- Loebstein, R., Mahagna, R., Maor, Y., Kurnik, D., Elbaz, E., Halkin, H., Olchovsky, D., Ezra, D., Almog, S., 2008. Hepatitis C, B, and human immunodeficiency virus infections in illicit drug users in Israel: prevalence and risk factors. *Isr. Med. Assoc. J.* 10, 775–778.
- Neumark, Y., Friedlander, Y., Bar-Hamburger, R., 2002. Family history and other characteristics of heroin-dependent Jewish males in Israel: results of a case-control study. *Isr. Med. Assoc. J.* 4, 766–771.
- Ott, J.J., Paltiel, A.M., Becher, H., 2009. Noncommunicable disease mortality and life expectancy in immigrants to Israel from the former Soviet Union: country of origin compared with host country. *Bull. World Health Organ.* 87, 20–29.
- Peles, E., Schreiber, S., Adelson, M., 2010. 15-Year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. *Drug Alcohol Depend.* 107, 141–148.
- Sanchez-Carbonell, X., Seus, L., 2000. Ten-year survival analysis of a cohort of heroin addicts in Catalonia: the EMETYST project. *Addiction* 95, 941–948.
- Shiels, M.S., Cole, S.R., Mehta, S.H., Kirk, G.D., 2010. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. *J. Acquir. Immune Defic. Syndr.* 55, 510–515.
- Walboomers, J.M., Jacobs, M.V., Manos, M.M., Bosch, F.X., Kummer, J.A., Shah, K.V., Snijders, P.J., Peto, J., Meijer, C.J., Muñoz, N., 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J. Pathol.* 189, 12–19.
- Wilson, M., Daly, M., Pound, N., 2002. In: Pfaff, D.W., Arnold, A.P., Etgen, A.M., Fahrbach, S.E., Rubin, R.T. (Eds.), *An Evolutionary Psychological Perspective on the Modulation of Competitive Confrontation and Risk-Taking*. Academic Press, San Diego, CA, pp. 381–408.
- World Health Organization, 1993. *The ICD-10 Classification of Mental and Behavioral Disorders. Diagnostic Criteria for Research*. WHO, Geneva.