MORTALITY IN PATIENTS OF METHADONE AND HEROIN MAINTENANCE THERAPY IN GERMANY AND SWITZERLAND

SWISS TEAM:

Ulrich Frick (1) (2), Jürgen Rehm (1) (3) (4) (5), Miriam Gerlich (1), Carlos Nordt (6), Rudolf. Stohler (6),

(1) Research Institute for Public Health and Addiction, Zurich, Switzerland
(2) Carinthia Univ. of Applied Sciences, Feldkirchen, Austria
(3) Centre for Addiction and Mental Health, Toronto, Canada
(4) University of Toronto, Canada
(5) Technische Universität Dresden, Germany
(6) Psychiatric University Hospital, Zurich, Switzerland

GERMAN TEAM:

Peter Raschke, Christina Hartwig, Peter Degkwitz, Axel Heinemann, Christian Haasen

Centre for Interdisciplinary Addiction Research, Hamburg, Germany

Zurich, Hamburg, Toronto

December 2007

Acknowledgements:

The authors would like to thank Continuum Health Partners, Inc. / International Center for Advancement of Addiction Treatment, Baron Edmond de Rothschild Chemical Dependency Institute of Beth Israel Medical Center for financial support of the study.

The Swiss team would like to thank the deputy medical officer of health for the canton of Zurich, Dr. P. Wyss for his kind assistance as well as the Fachstelle für Aids- und Suchtmittelfragen (Ms. M. Schmidt; A. Stoppa). Further thanks go to Mr. E. Wuest from the Swiss Federal Office for Statistics for supplying statistical data on mortality.

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This report is basically divided into four parts: after a general introduction and a background chapter on opioid dependence and mortality, two parts with the empirical results follow: first the report on the Swiss samples and then the report on the German samples. It concludes with a short overall discussion of the results.

BACKGROUND: OPIOID ADDICTION AND MORTALITY

There are different ways in which illicit opioid use may be implicated in fatal outcomes, which can be best described by direct and indirect effect paths. The most important direct effect path for mortality is that of fatal drug poisonings in the form of drug overdose deaths. Indirect pathways can be described as effects mediated by different forms of disease caused by drug use, with fatal outcomes (e.g., a sequence of drug use leading to HIV infections, leading to AIDS, and subsequently to death). Both forms of pathways will be described in detail below.

Overall, the mortality of illicit opioid drug users has been markedly higher than the mortality of the general population. Following a meta-analysis by English et al. (1995) (1), the standardized mortality ratio of injection opiod drug users age 15 to 34 years was 13.2 (95% CI 12.3-14.1). In other words, opioid injectors were found to have a mortality risk 13-fold greater than that of the general population when matched by age and sex.

Several studies have quantified the elevated mortality rates for so-called 'high risk' drug users, e.g. Injection Drug Users (IDUs) including but not limited to illicit opioid users. In a recent analysis, Degenhardt et al. (2004) (2) estimated the average annual death rate for problem drug users – defined mainly as drug injectors – to be 1.12% (95% CI between 0.78% and 1.46%), and other studies have identified an annual mortality rate of 0.5% - 2.0% among heroin use populations (Darke & Hall, 2003, Hser et al., 2001; Darke et al., 2007) (3-5). In Switzerland in the early 1990s, the annual mortality rate was estimated to be higher, around 2.5% to 3%, irrespective of treatment participation (Estermann, 1996; Rehm, 1995) (6;7).

Overdose deaths explain a large portion of these deaths. People who die accidentally from drug overdoses tend to be young adults with a mean age in the late 20s to early 30s, are overwhelmingly male, and usually have several years of drug use experience. Most are daily or almost daily users of drugs and the majority administer drugs by injection (Darke et al., 2007). (5). In addition, poverty, homelessness, co-administration of alcohol, benzodiazepines, antidepressants, concurrent use of other illicit drugs, recent changes in patterns of use affecting tolerance to drug (e.g., recent release from prison, enforced or voluntary abstinence, other treatment), impaired physical health status of the user, depression, and history of drug overdose during one's lifetime are all factors associated with greater risk for overdose death (Darke & Zador, 1996; O'Driscoll et al., 2001; Warner-Smith et al., 2001; Darke et al., 2007) (5;8-10).

Recently, particular attention has been given to increasing numbers around the world of overdose deaths related to opioids (Drummer, 2005) (11). A challenging aspect within these toxicological observations is to attribute causality for mortality to specific drugs found within the blood system. In most instances, however, this is difficult since the presence of a single drug in overdose deaths is quite rare. In this context, numerous jurisdictions have reported increases in mentions of methadone among drug overdose cases, although these increases in many instances likely reflect greater exposure of drug users due to expanded treatment access rather than an amplified role of methadone in causing deaths. Considerable recent concern has been raised by greatly increased numbers of overdose deaths especially in the US, in which prescription opioids have been implicated, surpassing the overdose death numbers (for 2002) for both cocaine and heroin deaths, respectively (Paulozzi et al., 2006) (12). However, given the overall lower availability of prescription opioids in Central Europe compared to North America (International Narcotics Control Board, 2006) (13), this factor should be less important in this region.

Other injuries are also associated with illicit opioid use, both unintentional and intentional injury. Violence to others, including homicides, tends to be elevated due to the illicit nature of opioid use. However, among patients in treatment in Central Europe, this cause of death is less likely than in some North American contexts (e.g. Rehm et al., 2005) (14). More important are suicides (e.g. Popova et al., 2006) (15). The rates of completed and attempted suicide among illicit drug users are many magnitudes higher than those in the general population (Darke et al., 2007; Hulse et al., 1999)(5;16). Data from six study sites in five US cities has demonstrated that approximately 36% of IDUs have suicidal ideation, while 7% of the individuals surveyed attempted suicide in the 6 months prior to enrolment (Havens et al., 2004). Illicit drug users have substantially higher levels of risk factors for suicide than the general population, including psychopathology, family dysfunction, social problems, social isolation and social dysfunction. In addition, polydrug use, which is very common among opiod users, has been specifically identified as a risk factor for suicide (Darke et al., 2007) (5).

Finally, infectious disease plays an important role as a cause of death in opioid users. Unsafe injection practices, unsafe sexual contacts, and multiple daily injections place IDUs at elevated risk for various infectious diseases, such as HBV, HCV and HIV infection (Fischer et al., 2004; March et al., 2007; UNAIDS, 2002; Wylie et al., 2006) (17-20). While prevalence rates vary by country, in many developed countries HCV rates are above 50% for IDUs. For example, the prevalence of HCV among IDUs in the United States varies from 80% to 95% (Edlin, 2002)(21), in Canada from 16% to 88% (Bowker et al., 2004; Ford, 1999) (22;23), in Australia from 50% to 60% (Doab et al., 2005) (24) and in Europe is over 60% (EMCDDA, 2003) (25). HIV rates tend to be lower, and have larger inter-country variability. In addition to the elevated risks for infectious disease in IDUs, there is also a high prevalence rate of co-morbidity between the different infectious diseases. As a prior analysis on Swiss patients in heroin-assisted maintenance treatment (HAMT) has shown, infectious diseases were an important cause of death especially in the early phase of the program in the mid 1990s (Rehm et al., 2005) (14).

Given the above relations, we expect a greater mortality of German and Swiss patients in maintenance treatment. The aim of this contribution is to quantify the exact magnitude of this mortality and discuss some implications.

MORTALITY IN SUBSTITUTION TREATMENT IN THE CANTON OF ZURICH

METHODS AND SAMPLE

There are two case registers in the canton of Zurich, one for HAMT and one for methadone maintenance treatment (MMT). Both registers for reason of data safety operate on an anonymous basis using treatment episodes as sampling units. Subjects undergoing multiple treatment episodes in both registers can be identified by means of two separate anonymous unique person numbers which are not interchangeable between registers.

Data on deaths of patients while under HAMT in the canton of Zurich (approximately 1,3 million inhabitants) were collected from the national treatment register that has been run by the Research Institute for Public Health and Addiction (RIPHA), Zurich, since 1994. In the canton of Zurich, six outpatient treatment centers were responsible for HAMT during the study period, three of which were located within the city of Zurich. Completeness of the HAMT register data has been ascertained at 100%, because each single patient has been requiring a formal approval from the Swiss Federal Office of Public Health before entering treatment. After a continuous increase of the number of annually treated patients from n=152 (in 1994) to 406 patients in 2002, numbers remained stable at a level of about 420 treated patients per year. Stabilization of patients' living situations and health status, as measured by the average number of annual days a patient received his/her substitution medication, continuously improved from 187 days per patient in 1994 to 320 days per patient and year in 2006 (see Rehm et al., 2001 (26), for a general description of HAMT and its effectiveness in Switzerland).

A comparable treatment register for methadone maintenance treatment (MMT) has been run in the Canton of Zurich since 1991 (Nordt & Stohler)(27), collecting data during the

period 1998 and 2003 from 27 outpatient substitution clinics and from 446 doctors in private practice.. The number of patients under MMT in the canton of Zurich remained at a stable level of about 3700 annual subjects within this reporting period. The average number of days that a patient received the substitutive medication increased slightly from about 260 days in 1998 to about 290 days in 2003. Deaths under MMT were identified and ascertained by the following procedure:

1) All 251 deaths reported directly to the MMT-register were preliminarily counted with patients sex, initials, and date of death.

2) Independently from this first list, a second source was used to validate the number of deaths: As there exists a compulsory registration of deaths of substituted patients, the respective paper files of the cantonal health authorities were screened and a second list containing n=164 cases was collected. Deaths were transmitted with sex, initials, birth date, and date of death.

3) There were 134 deaths with identical key variables on both lists. N = 117 cases were only counted by the treatment register. Additional n=30 cases stemmed from the cantonal files only.

4) A third list with the unique treatment numbers of all 2283 patients leaving MMT during the study period without ascertained subsequent treatment of the patient either in abstinence oriented or in HAMT (including cases with reported deaths) was used to cross-check those deaths not overlapping in step 3. A manual search procedure revealed in 20 of 30 cases stemming exclusively from the cantonal paper files that these cases indeed matched to one of the n=117 deaths reported exclusively to the MMT register. Mostly a mismatch of initials (lastname and forename had changed) was responsible for double counting these cases. Thus, underreporting of deaths in the MMT register was estimated as occurring in 10 of a total of 261 deaths (3.8%).

5) From the Swiss Federal Statistics Bureau, which is responsible for the registry of death certificates, causes of death were ordered for deceased patients. Data quality was not sufficient for further analysis both with respect to completeness of cases and with quality of registered causes. For instance, there were numerous cases registered with a cause “exitus letalis” or other non informative reasons.

Age groups for mortality analysis were 18 to 34 years, 35 to 44 years, and 45 to 69 years. Age was calculated as current age at the beginning of each year of observation. Weights for direct standardization of mortality rates were calculated according to the total treatment population of HAMT (complete Switzerland; person years) in 2006.

Table 1: Weights used for Switzerland

Sex	Age	Weight
Men	< 34 y	0,1944
	35-44 y	0,4257
	45-69 y	0,1383
Women	< 34 y	0,0712
	35-44 y	0,1348
	45-69 y	0,0356
	SUM	1

Age-sex specific mortality rates under both treatment modalities were compared to the respective mortality of the Swiss total population, using the WHO mortality database (http://www.who.int/whosis/mort/download/en/index.html; data as of November 2006) as a basis for calculations. Age groups for the denominator of Mortality Ratios had to be determined slightly deviating among the youngest group as 20-34 years, 35-44 years, and 45-69 years, because WHO stores data only in 5-year age groups. Exact confidence limits for mortality rates were calculated using SAS-macro "bnmlci.sas" by Erik Bergstralh of the Mayo Clinic College of Medicine, which is freeware and can be downloaded from http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm.

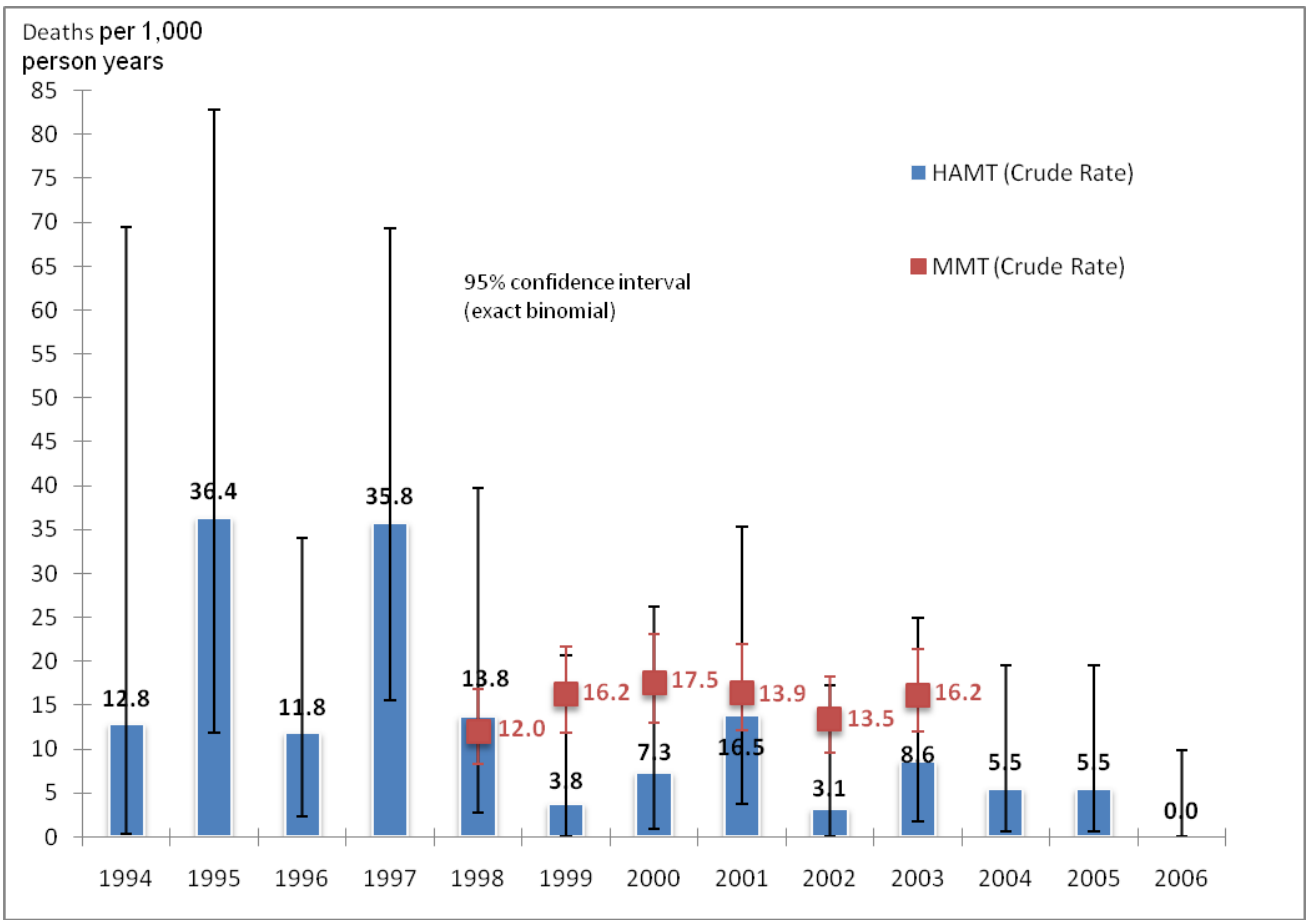
Confidence intervals for directly standardized (age, sex) mortality rates were calculated assuming a Poisson distribution of deaths and using Chiang's normal approximation to Poisson

rate sums (Chiang 1961;Armitage & Berry 1994; Armitage et al. 2002) (28-30). Because this method originally was constructed to standardize a rate from a second sample into the age proportion of the first (the reference) sample, and because we used proportions from a third population, i.e. HAMT treatment population of complete Switzerland, for standardization, the sample sizes in the respective formulas were taken from Zurich's HAMT resp. MMT treatment groups in order to reflect the limited sample sizes and the resulting uncertainty correctly. The confidence intervals for the standardized mortality ratio were taken from the textbook of (Rothman & Greenland 1998). (31)

RESULTS

The following Figure 1 gives an overview of crude rates of death in MMT and HAMT in the Swiss samples. Most of the yearly rates are within the limits of the usual results, ie., within a band of mortality rates between 0.5% and 2.0% (see above).

Figure 1: Crude mortality rates per 1,000 person years in substitution therapy (canton Zurich)

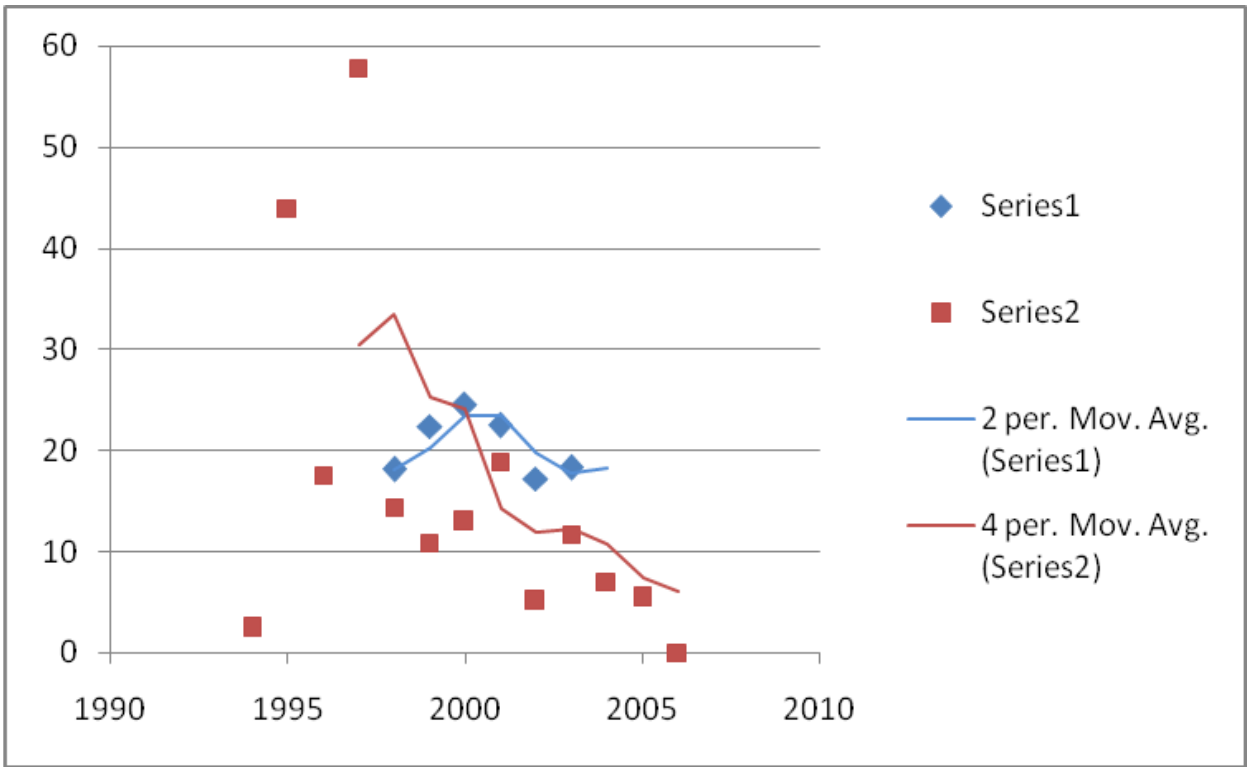


Crude mortality rates were lower than the rates in the early 1990s in Switzerland, however, which were between 2.5% and 3%, irrespective of treatment status (Estermann, 1996; Rehm, 1995) (6;7). The two exceptions above this band were the years 1995 and 1997 for HAMT with rates above 3%. The higher mortality rates in the early 1990s were in part due to AIDS deaths (Rehm et al., 2005)(14), with the rates in later years reflecting the survivors of a major drug-related AIDS wave.

Please note, however, that rates for deaths of HAMT patients had been based on small numbers and thus showed high variability. More details on age-and-sex-specific rates can be obtained from the authors upon request.

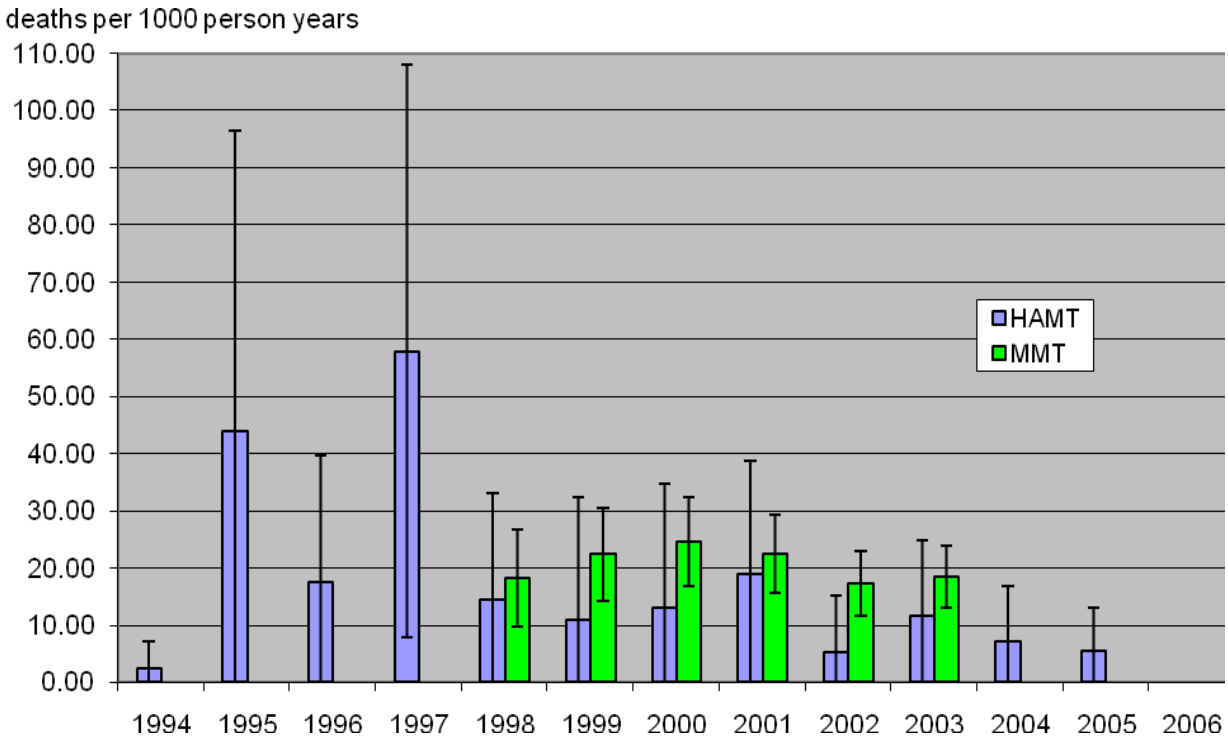
In the core data period 1998 to 2003, where data were available for both HAMT and MMT, HAMT seems to be associated with lower mortality rates, but the confidence bands for MMT were almost entirely within the confidence bands for HAMT (see Figure 1). Thus, the seeming difference between HAMT and MMT may be entirely due to chance. Also, differences in crude rates could also be due to different age distributions in the samples. This factor was adjusted for with standardization.

Figure 2: **Sex- and age-adjusted mortality rates per 1,000 person years in substitution therapy (canton Zurich; standardized to age distribution of HAMT population 2006)**



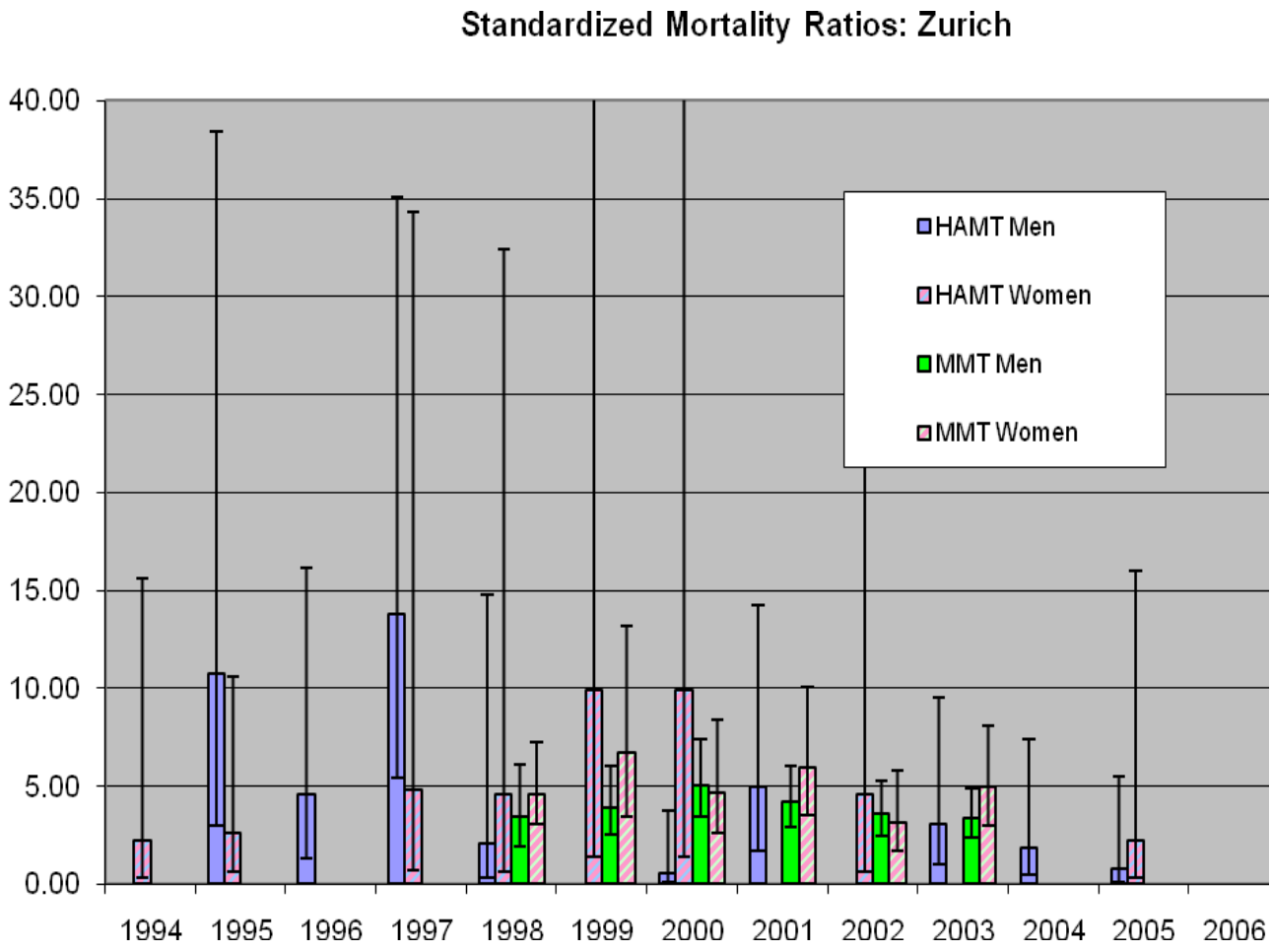
Overall, a downward mortality trend for HAMT can be seen in the moving averages, especially after 2000, and a less steep decrease of mortality in MMT as well. The sex- and age-standardized rates also seemed to indicate, that the patients in MMT had a higher mortality rate than the HAMT patients. As the base numbers did not change, however, the cautious remarks regarding the small sample sizes for HAMT given above still apply (see overlapping confidence intervals in Figure 3).

Figure 3: **Sex- and age-adjusted mortality rates per 1,000 person years and their confidence intervals in substitution therapy (canton Zurich; standardized to age distribution of HAMT population 2006)**



Standardized mortality ratios are shown in Figure 4. Overall, patients in substitution therapy show higher mortality than the general population, but markedly lower SMRs compared to the meta-analyses of English and colleagues (1995). In other words: compared to the general population, there still is a relative higher mortality, but the gap is not as large as it had typically been in the 1980s and early 1990s.

Figure 4: **Standardize mortality ratios for patients for opioid dependence by year, sex and type of substitution treatment**



DISCUSSION

For the canton Zurich and for Switzerland as a whole, the mortality rates among drug opioid addicts, which had been relatively high in the early 1990s with rates between 2.5% and 3%, have come down in recent years. This was especially true for patients in HAMT, where current rates have become almost as low as the general population. This is all the more astonishing, as the cohort of patients in HAMT has been aging almost monotonically with relatively low turnover rates and low incidence in younger age cohorts (Gschwend et al., 2003 (32); yearly report of HAMT by the Swiss Federal Office of Public Health http://www.bag.admin.ch/themen/drogen/00042/00629/00798/01191/index.html?lang=de). Thus, the average age of patients in HAMT had been less than 31 years in 1994 and was more than 35 years in 2006. As mortality is closely related to age, one would expect increasing mortality rates.

What are possible explanations for the declining mortality rates? We believe, that two processes interact to produce this effect. First, the incidence of opioid addiction has been declining since the early 1990s (Nordt & Stohler 2006) (27) and as a result, the cohort of treated opioid users has been relatively stable, and aging. Within this cohort, many of the people with the most severe risk factor profiles died in the early 1990s, in part from AIDS (Rehm et al., 2005) (14). The remaining cohort, even though opioid using, has relatively lower risk profile, plus was integrated into a comprehensive treatment system in the canton of Zurich as in the rest of Switzerland, with wide availability of methadone maintenance treatment, availability of other opioid maintenance therapy including HAMT, wide availability of harm reduction measures such as supervised injection sides and a well-developed social care system (Klingemann, 1998; www.bag.admin.ch). As a result, opioid-attributable mortality rates

dropped, and the rates of this population are no longer that dissimilar to the rates of the general population.

REFERENCES

Reference List

(1) English D, Holman C, Milne E, Winter M, Hulse G, Codde G, Bower G, Corti B, de Klerk N, Knuiman M, Kurinczuk J, Lewin G, Ryan G. The quantification of drug caused morbidity and mortality in Australia 1995. Canberra, Australia: Commonwealth Department of Human Services and Health; 1995.

(2) Degenhardt L, Hall W, Warner-Smith M, Lynskey M. Illiicit drug use. In: Ezzati M, Lopez A, Rodgers A, Murray CJL, editors. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Volume 1 ed. Geneva: World Health Organization; 2004. p. 1109-75.

(3) Darke S, Hall W. Heroin overdose: research and evidence-based intervention. J Urban Health. 2003; 80(2):189-200.

(4) Hser Y, Hoffman V, Grella C, Anglin M. A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry. 2001; 58(5):503-8.

(5) Darke S, Degenhardt L, Mattik R. Mortality amongst illicit drug users: epidemiology, causes and intervention. Cambridge: Cambridge University Press; 2007.

(6) Estermann J. Sozialepidemiologie des Drogenkonsums. Zu Prävalenz und Inzidenz des Heroin- und Kokaingebrauchs und dessen polizeiliche Verfolgung. Berlin: Springer; 1996.

(7) Rehm J. Situation sociale des consommateurs de drogues. In: Fahrenkrug H, Rehm J, Müller R, Klingemann H, Linder R, editors. Drogues illégales en Suisse, 1990-1993. Zürich: Seismo; 1995. p. 35-54.

(8) Darke S, Zador D. Fatal heroin "overdose": a review. Addiction. 1996; 91:1764-72.

(9) O'Driscoll P, McGough J, Hagan H, Thiede H, Critchlow C, Alexander E. Predictors of accidental fatal drug overdose among a cohort of injection drug users. Am J Public Health. 2001; 91(6):984-7.

(10) Warner-Smith M, Darke S, Lynskey M, Hall W. Heroin Overdose: causes and consequences. Addiction. 2001; 96:1113-25.

(11) Drummer O. Recent trends in narcotic deaths. Therapeutic Drug Monitoring. 2005; 27(6):738-40.

(12) Paulozzi L, Budnitz D, XI Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf. 2006; 15(9):618-27.

(13) International Narcotics Control Board. Narcotic drugs: estimated world requirements for 2007: statistics for 2005. New York: INCB; 2006.

(14) Rehm J, Frick U, Hartwig C, Gutzwiller F, Gschwend P, Uchtenhagen A. Mortality in heroin-assisted treatment in Switzerland 1994-2000. Drug Alcohol Depend. 2005; 79(2):137-43.

(15) Popova S, Rehm J, Patra J. Illegal drug-attributable mortality and potential years of life lost in Canada 2002: implications for prevention and policy. Contemp Drug Probl. 2006; 33(3):343-66.

(16) Hulse G, English D, Milne E, Holman C. The quantification of mortality resulting from the regular use of illicit opiates. Addiction. 1999; 94(2):221-9.

(17) Fischer B, Haydon E, Rehm J, Krajden M, Reimer J. Injection drug use and the hepatitis C virus: Considerations for a targeted treatment approach-The case study of Canada. J Urban Health. 2004; 81(3):428-47.

(18) March J, Oviedo-Joekes E, Romero M. Factors associated with reported hepatitis C and HIV among injecting drug users in ten European cities. Enfermedades infecciosas y microbiologi´a cli´nica. 2007; 25(2):91-7.

(19) UNAIDS: The Joint United Nations Programme on HIV/AIDS. Report on the Global HIV/AIDS Epidemic 2002. Geneva, Switzerland; 2002.

(20) Wylie J, Shah L, Jolly AM. Demographic, risk behaviour and personal network variables associated with prevalent hepatitis C, hepatitis B, and HIV infection in injection drug users in Winnipeg, Canada. BMC Public Health. 2006; 13(6):229.

(21) Edlin BR. Prevention and treatment of hepatitis C in injection drug users. Hepatology. 2002; 36(5 Suppl.1):S210-S219.

(22) Bowker SL, Soskolne CL, Houston SC, Newman SC, Jhangri GS. Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in a Northern Alberta population. Can J Public Health. 2004; 95:188-92.

(23) Ford PM, Queen's University HIV Study Group. HIV/AIDS in prisons: HIV and Hepatitis C seroprevalence and associated risk behaviours in a Canadian prison. HIV/AIDS Policy and Law. 1999; 4(2/3).

(24) Doab A, Treloar C, Dore G. Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia. Clin Infect Dis. 2005; Suppl.5:S313-S320.

(25) EMCDDA European Monitoring Centre for Drugs and Drug Addiction. Annual Report: State of the Drugs Problem in the European Union and Norway. Lisboa: EMCDDA; 2003.

(26) Rehm J, Gschwend P, Steffen T, Gutzwiller F, Dobler-Mikola A, Uchtenhagen A. Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study. The Lancet. 2001; 358:1417-20.

(27) Nordt C, Stohler R. Incidence of heroin use in Zurich, Switzerland: a treatment case register analysis. The Lancet. 2006; 367(9525):1830-4.

(28) Chiang C. Standard error of the age-adjusted death rate. US Department of Health, Education and Welfare: Vital Statistics Special Reports. 1961; 47:271-85.

(29) Armitage P, Berry G. Statistical Methods in Medical Research (3rd edition). Oxford: Blackwell; 1994.

(30) Armitage P, Berry G, Matthews J. Statistical Methods in Medical Research (4th edition). Oxford: Blackwell Science; 2002.

(31) Rothman K, Greenland S. Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998.

(32) Gschwend P, Rehm J, Eschmann S, Uchtenhagen U. Heroingestützte Behandlung für Opioidabhängige in der Schweiz von 1994 bis 2001 - Inanspruchnahme und Charakteristik der Ein- und Austretenden. Das Gesundheitswesen. 2003; 65(2):75-80.

MORTALITY IN SUBSTITUTION TREATMENT IN GERMANY

OBJECTIVE

The objective is to determine mortality rates in heroin dependents under methadone maintenance treatment (MMT) compared to heroin-assisted maintenance treatment (HAMT) in Germany. Experience with methadone substitution goes back to the 1990s, for heroin experience has been gained since the year 2002.

In Germany, maintenance treatment with methadone was discussed very controversially, and even more maintenance treatment with heroin. Therefore, the carrying out and initiation of maintenance treatment was strongly influenced by existing norms and the resolutions were most often passed in line with party politics. However, there were some exceptions. Federal states or cities which suffered most from the drug problem – e.g. Frankfurt or Nordrhein-Westfalen – decided early in favor of maintenance treatment, often in opposition to the party line; other states – Hamburg in particular – pushed maintenance treatment in line with party politics. The result was a German-wide patchwork of acceptance and introduction of maintenance treatment both for methadone and heroin maintenance.

Meanwhile, methadone has been accepted as standard medication for maintenance treatment in Germany, at least if the indications are fulfilled. Heroin has been recognised as effective based on a multicentre – Munich, Karlsruhe, Bonn, Frankfurt, Cologne, Hanover, Hamburg – clinical study (Haasen et al. 2007), but it has not yet been introduced all over Germany.

This has implications on the data collection of the present study.

- For the maintenance substance heroin, data were only available from the cities which participated in the scientific clinical study.
- For the maintenance substance methadone, data are now available from all federal states and overall data for Germany.

As the ZIS is the institute responsible for the German-wide multi-centre heroin trial, there are no barriers concerning data collection for heroin maintenance treatment. The relevant publications are available and were forwarded to the Swiss institute. The data can be analysed there according to the formulated questions. There is, of course, the limitation that the data are only valid for this scientific trial. The advantage, on the other hand, consists in the fact that this study had been carried out under extreme international control.

The situation is different for the data on methadone maintenance treatment. Extensive research was conducted in the 1990s (Raschke 1994). Regarding mortality rates among substituted and non-substituted drug dependents, two articles (Heinemann et al. 1999, Raschke et al. 2001) are of particular importance.

Meanwhile, however, methadone maintenance became a standard treatment and the indication and application are subjected to new regulations. This requires new data collection and analysis for the period since 2000. No original scientific investigations were conducted, but information on methadone maintenance treatment is centrally accumulated and managed. The investigation and registration of drug deaths has always been the responsibility of the individual federal states. This is the task of the criminal authority in each state (LKA) and of the institutes of forensic medicine.

Since the central registration of maintenance treatment is done at the level of the federal states and the registration of drug deaths equally occurs within the state boundaries,

and since both institutions act independently of each other, problems of data collection are to be expected. This will be discussed in the next paragraph.

DATA COLLECTION AND DATA PROTECTION IN METHADONE MAINTENANCE TREATMENT

There exists a centre responsible for the German-wide registration of the names of patients currently in maintenance treatment (Bundesopiumstelle), with the objective to avoid double treatments. However, this centre is very well guarded by data protection and data is stored only for six months. Despite repeated attempts, this valuable data source proved to be unproductive for the present scientific question, even if an approval of the scientific goals would have been accepted.

Therefore, it was only possible to recur to sources at federal state levels. These are the registers of the associations of health insurances (KV), which register within their catchment area which members receive maintenance treatment by which doctors. This register seems to be rather valid as recompensation claims can be based on it and it serves to avoid double prescriptions.

These registers include a.o. the name of the insured person, the beginning and the end of the respective treatment period, possibly the initial start of treatment, sometimes the reason for terminating treatment – termination by the patient, down-dosing and abstinence of the patient, moving away, death etc. – or other information. As a rule, this information is not always available, is scare or is not passed on for reasons of data protection. Therefore, the data base is organised in a very federalistic way.

Because of the scientific question, only the 11 old federal states (those existing in West Germany prior to unification of the two Germanys in 1990) could be considered, as their heroin problems and the existing practice of maintenance treatment evolved over a longer period. However, the associations of health insurances of these 11 states are not organised according to state boundaries, as there are more associations (KV) than there are states, e.g. two in Baden-Württemberg and two in Nordrhein-Westfalen.

Each federal state has a person responsible for data protection, who has to follow the respective law on data protection valid in his state. At each KV there is a person responsible for data protection, who has to observe the federal laws and as well as the laws of the federal state. And each person in charge interprets differently whether information can be passed on anonymously for scientific aims and if yes, what type of information. Unfortunately the different interpretation of data protection laws led to the situation that we were only able to receive certain data sets (see attached Excel-Document “Mortality_tables_figures.xls”; spreadsheet “data sets”).

For the objective of the present investigation, it was important not only to find out who was substituted and when, but also with what results. In the framework of a mortality study, this involves questions concerning the death of patients.

“Drug death” involves particular registration procedures of the (LKA) – either due to the circumstances of finding the dead person or due to examinations by forensic medicine. Reporting a “drug death” is an official act on the part of the LKA. This is not always registered in the KV register – either because this death is not reported to the KV or is not registered by it, or because the responsible doctor does not report it or because death occurs only long after maintenance treatment. Congruent information on drug deaths is neither assured nor systematically intended.

However, if the investigation focuses on mortality, information from the LKA is indispensable, as this is the place where at least “conspicuous” deaths - overdose, suicide, “accidents” - are registered and examined - mostly by forensic medicine. Therefore, ***both*** sides of the information are necessary: from the KV for matters of maintenance treatment, from the LKA for matters of possible drug deaths. There is a tendency that substituted patients dying from subsequent illnesses such as AIDS or other illnesses fall through the mesh of this double filter, unless they are (not necessarily) registered in the register for maintenance treatment of the KV.

The LKA as well have their own person in charge of data protection, with his own state or federal opinions. Sometimes, they can be persuaded and sometimes not - for whatever reason.

Faced with this network of different opinions, oppositions and institutional worries in a variety of institutes, scientific work with the intention of clarifying facts and assessing the consequences of facts is forced to be content if, after many efforts, a sufficient number of well-meaning persons are found to warrant the establishment of a database that allows valid analyses.

DATA BASIS

The main pillars of the present study are the federal states – Berlin, Hamburg and Hessen – which provided the corner stones, i.e. data on official drug deaths according to the respective LKA, and data from the register of maintenance treatment of the KV. This allows a valid comparison of both data sets with regard to whether heroin use was substituted within a

defined period of time and whether the patient died during maintenance treatment. This allows valid estimations of the mortality rate under the conditions of maintenance treatment.

Mainly the Hamburg data allow a valid estimation of the unreported cases, in order to determine the number of non-substituted heroin users and combine them with the non-substituted drug deaths. Thus, the mortality rates of substituted and non-substituted heroin users can be compared. These complicated calculations have not yet been carried out.

Similarly, based on the heterogeneous data transmission by the LKAs and the KVs – ranging from detailed information on the cause of death to detailed information on the termination of maintenance treatment – numerous specific data analyses are imagined and partly planned, though they could only be done for individual federal states. Such analyses are considered but do not directly touch the central objective of the present analysis.

The presented data are mainly concerned with the comparability of the data from the three selected states – Berlin, Hamburg and Hessen – despite the heterogeneous state of information. With an estimate of 30,000 to 40,000 heroin users, they represent a considerable proportion of the German heroin problem, and Hamburg and Hessen (Frankfurt) were traditionally the first to implement an expansive maintenance practice. Therefore, the presented data are not representative according to sampling rules, but they represent an important part of the population investigated by this study.

To stress this aspect, the three areas of investigation are combined – apart from individual reports: on the one hand focusing on the period between 2002 and 2006 (data from the LKAs and KVs are available); on the other hand on the aspect whether the drug death occurred during or after maintenance treatment.

BASIC DATA

The basic data for the three federal states are presented in table 1 (see attached Excel-Document “Mortality_tables_figures.xls”; spreadsheet “Overview”).

The 5-year period of observation for Hessen and Berlin was from 2002 to 2006 and for Hamburg 1999 to 2005. This corresponds to a total of 17 years of observation in regions markedly distant from each others, so that migration between these regions can be excluded to a large extent.

In these 17 years of observation, the LKA registered 1,982 drug deaths according to the official definition. In addition, there were 189 deaths that were *only* registered by the KV. These are not necessarily drug deaths, as death did not occur in relation to drug use or drug-induced consecutive illness (e.g. AIDS), but for other reasons. But it is also possible that notifiable cases were not reported because it was not clear that the cause of death was related to drug use or perhaps the death was registered in another federal state. Therefore, the following analyses are mainly based upon “official” drug deaths. However, in terms of worst case and for the sake of information, mortality rates were also calculated as if these 189 deaths were drug deaths. (See Table 3 in the spreadsheets “Hessen” and “Berlin”).

Of the 1,982 drug deaths, 546 (27.5%) had participated in regular maintenance treatment at least for some time in the 17 years of observation. A total of 20,858 patients participated in maintenance treatment for a total of 48,171 treatment years within this period. There were marked differences between Hessen and Hamburg on the one hand and Berlin on the other hand. In Hamburg and Hessen, the number of opiate dependents in maintenance treatment was 2 to 3 times higher than in Berlin, although the state of Hessen with the metropolitan region of Frankfurt includes about 1 million inhabitants, Hamburg 1.7 and Berlin 3.4 million. This imbalance is not due to dissimilar strains caused by the drug problem, but due to different policies related to maintenance practice. Hamburg and Hessen are among the

precursors with regard to the implementation of maintenance treatment and facilitation of access, the attitude of Berlin was rather reserved or even negative. Therefore, it was a matter of course for Frankfurt and Hamburg to participate in the multi-centre heroin trial, while Berlin refused participation. Berlin's reticence regarding maintenance treatment is also reflected by the fact that only 18% of drug deaths in Berlin had been in maintenance treatment at some time, compared to 30% in Hessen and 40% in Hamburg – related to a slightly longer period of observation. This description is necessary in order to allow an adequate interpretation of the mortality rates.

For the evaluation of maintenance treatment with respect to mortality rates, the time of death is of importance, that is, whether death occurred during ongoing maintenance treatment or only after dropping out or after successful termination of the treatment. Of the 546 drug deaths, who had been for a certain time in maintenance treatment during the period of observation, 314 (57.5%) died during treatment or in the first 30 days after the reported termination of treatment, and 226 (41.3%) later. In 6 cases (1.1%) the time of death could not be ascertained.

Two perspectives are possible.

On the one hand, the avoidance of drug death can be considered as a primary target of maintenance treatment. From this point of view, it is irrelevant whether death occurred during or after treatment. Evidently, the treatment did not succeed in reaching sufficient retentive power or in avoiding critical situations. Therefore, the risk period corresponds to the entire treatment period (population at risk (person years)), even if treatment is interrupted for a certain time. Thus, the mortality risk is split: during or after treatment. This is shown by tables 2a and 2b for the three federal states (see spreadsheets in Excel-Document attached).

On the other hand, it could be taken into consideration that the reasons for treatment termination can vary considerably. They can be first indices of critical events and should then

be assigned to the first perspective. The termination or temporary interruption of treatment can also be due to moving away, switching the doctor, lack of continued approval, discontinuation by the doctor or regular termination after down-dosing towards abstinence. In this case time following a treatment phase is the actual time of risk or the phase of probation without maintenance substances, which might be a time of higher mortality risk. If, for instance, this is particularly high, it should be considered with respect to therapeutic responsibility to avoid such situations as far as possible. Therefore, this situation was represented in table 2c in the corresponding table sheets, population at risk being related to those periods of maintenance treatment where maintenance treatment is discontinued. These can be periods of abstinence as well as returns to the drug scene.

COMPARISONS BETWEEN THE FEDERAL STATES AND COURSE DEVELOPMENTS

TIME DEVELOPMENT

The basis is the crude rate (mortality (deaths per 1000 person years)) in the respective year of observation. The spreadsheet “diagram 1” shows that the mortality rate in Berlin is rather constant and markedly higher than in the other two states with a positive attitude towards maintenance treatment. In Hamburg, mortality is also relatively constant at a low level, comparable to Hessen, where a tendency to decline can be observed.

INFLUENCE OF AGE

With respect to age groups – up to 35 years, 35 to 45 years, 45 years and older –Hessen has the lowest crude rate and Berlin the highest in each case. However, this does not allow us to generalize that younger patients have a greater risk under maintenance treatment than older patients (see spreadsheet “diagram 2”).

The development of the mortality rates according to age groups within the federal states is also rather heterogeneous. In Hessen and Hamburg, mortality markedly decreases over time among the younger patients, among the middle age groups, this tendency continues in Hessen, but not in Hamburg, where the mortality rate decreases among older patients, which is not the case in Hessen. Overall, the tendency is positive, mainly for the younger patients. In Berlin, this tendency is not observed (see spreadsheet “diagram 3 to 5”).

MORTALITY RATE ACCORDING TO TIME OF DEATH

The closer the time of death is to treatment, the more this treatment is made “responsible” for the death. This is particularly true in case of overdose and less if the progressive course of AIDS, acquired through needle sharing, leads up to death. If the time of death is farther away from the termination of treatment, other circumstances can more easily be made responsible for the death. In any case, discontinuation of maintenance treatment in opiate dependents is always the beginning of a potentially critical time and the responsibility is therefore the treatment providers’, especially if treatment was discontinued too early. Therefore it is important to investigate mortality risks during and subsequent of treatment.

A comparison of the development of mortality rates during maintenance treatment (or within one month) in the three federal states (see table sheet “diagram 6”) shows a gratifying development: a decline in all three states. However, the level in Berlin is always clearly higher than in Hessen and Hamburg, where the levels are similar.

A comparison of the development of mortality rates according to maintenance treatment (see spreadsheet “diagram 7”), the picture is very different: Mortality declines in Hessen, is rather constant in Hamburg and is distinctly increasing in Berlin. This can be the

result of premature termination of treatment or a lack of retention power, or perhaps "difficult" patients have been shifted about.

A glance at the development of mortality rates – during or after MMT – within the different federal states provides some indications (see spreadsheets "diagram 8 to 10"). In Hamburg and even more so in Berlin, there are developments in opposite directions: Mortality declines during MMT, mortality increases after MMT. In Hamburg, both rates draw closer, in Berlin, mortality following MMT clearly gets ahead of mortality during. A possible reason could be that risk patients are "re-sorted" – away from maintenance treatment to non-treatment. However the example from Hessen (see spreadsheet "diagram 8") shows that this is not necessarily so: both mortality rates decline to similar levels.

This indicates that it is advisable to maintain maintenance treatment rather for a longer period.

MORTALITY AND CRITICAL TIMES

Up to now, all analyses assumed that the population at risk measured in person years is related to the persons and the periods of maintenance treatment. Now the critical time is measured according to the periods when a patient ever treated was not treated within the period of observation, or in other words, the length of time when this person was not in maintenance treatment. This is the basis for calculating the risk to die within this phase of non-treatment. The results for Hessen and Hamburg are presented in the diagrams 11 and 12.

Both diagrams show that the risk of patients in maintenance treatment to die during a phase of treatment is much lower than to die during phase of non-treatment. Therefore, it is

necessary to avoid these phases or to manage them in a way that such critical times occur less often.

It is therefore necessary to obtain more information on the reasons for a (temporary) discontinuation of maintenance treatment and to refer them to mortality. This could be of benefit both for the practice and for politics regarding maintenance treatment.

REFERENCES

Haasen C, Verthein U, Degkwitz P, Berger J, Krausz M, Naber D: Heroin-assisted treatment for opioid dependence: a randomised, controlled trial. *British Journal of Psychiatry*, 2007; 191:55-62

Heinemann A, Iwersen-Bergmann S, Schmoldt A, Püschel K. Epidemiologische und toxikologische Aspekte der Drogenmortalität in Hamburg 1990 bis 1998. In: Krausz M, Raschke, P, Eds.; Drogen in der Metropole. Freiburg: Lambertus Verlag 1999

Raschke P, Heinemann A, Püschel K: Die Entwicklung der Rauschgiftmortalität 1990 bis 1998, *Hamburger Ärzteblatt* 2001; 80:70-77

Raschke P: Substitutionstherapie: Ergebnisse langfristiger Behandlung von Opiatabhängigen. Freiburg: Lambertus Verlag 1994

CONCLUSIONS

Overall, the following conclusions can be drawn from both studies:

1. Overall, the mortality rates in substitution treatment in Switzerland and Germany tend to confirm the range of mortality found in previous studies.

2. There seem to be stable differences between sites/regions. While these differences are within the confidence bands, and thus it cannot be excluded that they are due to chance, they are stable over different years. Thus, mortality rates in HAMT patients in the canton of Zurich were always lower than mortality rates for MMT for the years, where both rates could be compared in a standardized way; and mortality rates for MMT in Berlin were always higher than comparable rates in other provinces. At this point, we can only speculate about the reasons for these stable differences. The differences may be explained by specific procedures applied in different treatment centres, by the different drug scenes, by different pharmaceuticals used for substitution, or by different patient populations, or by a mixture of all of these factors.

3. Given the high variability among standardized the mortality rates in patient in different centres applying opioid substitution, one consequence should be increased quality control in substitution treatment and use of benchmarking, so the relatively less effective treatment centres can learn from the procedures of the more effective treatment centres.