One-year Mortality Rates of Patients Receiving Methadone and Buprenorphine Maintenance Therapy

A Nationally Representative Cohort Study in 2694 Patients

Michael Soyka, MD,‡ Sabine M. Apelt,† Martin Lieb, MD,* and Hans-Ulrich Wittchen, PhD†*

Abstract: Mortality rates in drug-dependent patients in substitution treatment remain a matter of debate. Although several retrospective toxicological or forensic postmortem studies on this issue have been conducted, few prospective studies have addressed this problem. In a nationally representative sample of 2694 opioid dependent patients in substitution treatment either with methadone or buprenorphine at baseline were monitored over a 12-month period (response rate, 91%). A total number of 1629 (60.4%) were still in treatment after 12 months. The overall mortality rate was 1.04%. In total, 28 patients of the initial sample deceased within the 1-year follow-up period. Eleven (0.4%) of these deaths are due to a fatal intoxication. Three patients (0.1%) died of human immunodeficiency virus/acquired immunodeficiency syndrome, and 3 (0.1%) committed suicide. Thirteen of these patients (4 with overdose/polyintoxication) were not in substitution treatment at the time of death. Other reasons included accidents and deaths due to other medical conditions. Only in one case the reason could not be ascertained. The mortality rate was similar in methadone as compared with buprenorphine patients. Taking into account the high comorbidity of opioid dependent patients and the severity of dependence, the mortality rate of approximately 1% confirms that maintenance treatment could be regarded as a fairly safe treatment.

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The prevalence of use of opioids including heroin has markedly increased over the last decades. Long-term studies among opioid addicts indicate a low abstinence and a high mortality rate.[1] Mortality of untreated heroin dependence is estimated at 1% to 3% per year, at least in 50% of cases attributable to heroin overdose[2,3] and, thus, 13 times higher than for the general population.[4] Dolan et al[5] found a mortality rate of 2% among untreated opioid dependent patients. Recently, Termorshuizen et al[6] reported follow-up data of a large sample demonstrating that at least 27% (probably 38%) of drug users had died within 20 years after starting regular drug use. Substitution treatment especially with methadone is one of the major treatment options for patients to reduce opioid consumption and increase retention in treatment, However, its effect on mortality is less clear ([7], for review see [8]). Few clinical studies reported mortality as an outcome measure. Although there are a number of toxicological or postmortem studies on drug fatalities in different regions and the role of substitution treatment in this respect[9–13] and also some retrospective analyses,[14] only one of the clinical studies reviewed by Amato et al[8] considered the outcome of patient mortality.[15] Although a number of clinical studies and meta-analysis found that methadone treatment overall reduce the risk of death significantly,[5,16–19] concerns about methadone-related deaths have increased with some conflicting results in the US[18]: As for North Carolina, Ballesteros et al[20] reported a strong increase in the death rate due to methadone in between years 1997 and 2001. Byrant et al[9] for New York City and Shah et al[21] for New Mexico could not replicate these findings. Similar concerns have been raised in various European countries such as Spain.[22]

In Germany, the overall number of deaths attributed to illicit drugs had increased in recent decades with a decline during the past 10 years from 1624 in 1994 to 1477 in 2003.[23] This decrease is probably due to a more widespread implementation of substitution treatment. Still a substantial number of deaths in drug dependence are attributed to fatal poisoning with methadone, mostly in combination with other drugs.[7] There is an obvious need for further studies in this field.[8,24]

In the Cost-Benefit and Risk Appraisal of Substitution Treatments (COBRA) study, we studied the 1-year mortality rate in a large representative sample of drug dependent patients in substitution treatment in routine care with respect to clinical characteristics.

METHODS

The COBRA study[26] is a nationally representative evaluation study based on a nationwide survey of substitution physicians in Germany. Background, aims, and methods of the COBRA study have been described in greater detail

*Psychiatric Hospital, University of Munich, Munich, Germany; †Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany and ‡Private Hospital Meiringen, Meiringen, Switzerland.

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Address correspondence and reprint requests to Michael Soyka, MD, Private Hospital, P.O. Box 612, CH-3860 Meiringen, Switzerland. E-mail: Michael.Soyka@pm-klinik.ch.

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elsewhere.[25–27] In this paper, we present the number of drug deaths associated with methadone or buprenorphine treatment and examine some clinical correlates by using the baseline and 1-year prospective follow-up data of the study.

Briefly, the study is a prospective-longitudinal, naturalistic, clinical epidemiological study in Germany with a comprehensive baseline, a 1-year clinical assessment and 2 additional intermediate cause assessments in between. The study is based on a national representative sample of originally 223 substitution physicians and a total of 2694 consecutive patients enrolled at baseline. Enrollment settings range from small primary care–based to large specialized substitution centers. Of the total of 2694 patients at baseline, 233 patients were lost during the 12-month observation period because of the fact that 29 participating physicians withdrew their study participation for various reasons. For these patients, no cause and outcome information was available. Detailed cause and outcome information was documented for 2461 patients corresponding to a conditional response rate of 91.4%.

Assessment

All patients completed a comprehensive baseline assessment, consisting of a patient questionnaire, a doctor's interview and questionnaire, and a standardized urine screening. A detailed description of the assessment tools and variables has been given in the previous methods publication.[26]

This paper reports descriptive information about the mortality rates by reason for death, type of substitution drug, sex, and current treatment status before the death occurred.

RESULTS

Subjects

Study participants were 2694 opioid-dependent men (68.4%) and women (31.6%). Mean age was 34.8 ± 8.1 years (range, 17–62 years), and 8.6% had another citizenship than German. Most participants (56.1%) were never married, 18.6% were separated or divorced, and 12.4% were currently married. Mean years of education was 11.1 ± 1.8 years (range, 1–20 years), and 53.9% were not used. Women (mean age, 34.1 ± 8.0 years) were slightly younger than men (mean age, 35.1 ± 8.1 years; odds ratio [OR], 0.984; P = 0.002) and had more years of education (women, 10.2 ± 1.8 years, vs. men, 10.0 ± 1.8 years; OR, 1.081; P = 0.001). The mean age at onset for any substance use (except nicotine) was 19.2 ± 3.9 years for men and 18.9 ± 3.8 years for women (OR, 0.980; P = 0.068). The mean age of the first substance use treatment was 23.9 ± 6.3 years for men and 22.2 ± 5.9 years for women (OR, 0.955; $P < 0.001$). With regard to treatment setting, 31.5%, 47.1%, and 21.4% of patients were treated in small, medium, and large settings, respectively. In total, 74.7% patients were treated with methadone, 24.6% with buprenorphine, and 0.7% (n = 19 patients) received other substitution drugs such as codeine. Patients had a wide range of additional somatic and mental disorders (diagnosed by the treating physician), for example, 5.9% human immunodeficiency virus (HIV), 61.4% hepatitis C virus, 36.2% with any somatic disorder, and 65.9% with any mental disorder.

Retention and Mortality Rates

Of the 2694 substitution patients who entered the study, 1629 (60.4%) were still in treatment after 12 months. For the 2461, information about course and outcome of the treatment was collected. Reasons for dropout were change of residence/physician (n = 254), disciplinary reasons (n = 120), abstinence (n = 100), switch to abstinence-oriented drug-free therapy (n = 174) or other/unknown reasons including lost to follow-up (n = 154). Two thousand thirteen (74.7%) of the 2694 patients received methadone and 662 (24.5%) buprenorphine.

During the 1-year follow-up phase, 28 patients (1.04%) had died. An overview of reasons for death can be found in Table 1.

Eighteen patients were men (64%) and 10 women (36%). Twenty patients were in the methadone group (71%), 7 in the buprenorphine group (25%), and 1 patient received another medication (codeine). With respect to fatal overdose/polyintoxication, 3 (27.3%) of 11 patients were treated with buprenorphine, 7 (63.6%) with methadone, and 1 (9.1%) with another medication.

TABLE 1. Reasons for Death in the COBRA Study

		Substitution Drug			Sex		Still in Treatment	
Reasons for Death	**Total**	**Buprenorphine**	**Methadone**	**Others**	**Male**	**Female**	**Buprenorphine**	**Methadone**
Fatal overdose/polyintoxication	11 (39.3%)	3	7	1	9	2	3	4
HIV/AIDS	3 (10.7%)	0	3	0	2	1	0	2
Accidents	3 (10.7%)	1	2	0	2	1	1	0
Infection/sepsis	3 (10.7%)	1	2	0	0	3	1	0
Suicide	3 (10.7%)	1	2	0	2	1	0	1
Carcinoma	1 (3.6%)	0	1	0	1	0	0	1
Other medical conditions	3 (10.7%)	0	3	0	1	2	0	1
Unknown	1 (3.6%)	1	0	0	1	0	1	0
Total	28 (100.0%)	7 (25.0%)	20 (71.4%)	1 (3.6%)	18 (64.3%)	10 (35.7%)	6 (21.4%)	9 (32.1%)

Of the 28 patients who died during the 1-year follow-up, 13 patients (buprenorphine group, n = 1; methadone group, n = 11; and codeine group, n = 1) were no longer in substitution treatment by the time of their death. Four died because of fatal overdose/polyintoxication, 1 because of HIV/acquired immunodeficiency syndrome (AIDS), 2 because of accidents, 2 because of an infection/sepsis, 2 committed suicide, and 2 patients died of the consequences of another medical condition.

DISCUSSION

The results from the COBRA study indicate a comparable low all-reason mortality rate of 1% in patients treated with buprenorphine and methadone. The most frequent reason was fatal overdose/intoxication of multiple substances. Other reasons for mortality were HIV/AIDS, suicide, or accidents.

It should be noted that 4 of the 11 patients who died of overdose/polyintoxication were not anymore in treatment at the time of their death for at least several weeks, indicating a very low mortality from overdose among patients in substitution treatment. There were no clear differences with respect to sex or substitution drug.

Few clinical studies have addressed mortality as an outcome measure.[8] Relevant data on this issue basically come from postmortem of toxicological studies.[9–13] These mortality rate data from an epidemiological study are basically in line with a number of those studies. Recent data from Hamburg, Germany, indicate that the mortality rate of patients in methadone maintenance program decreased to 0.7% in 2001 compared with 1.3% in 1992.[28] Seventy-one percent of those who died of methadone had not been in methadone maintenance program, indicating the fatal role of methadone on the black market.

Data from the US Drug Abuse Reporting program show a slightly higher death rate of 15 per 1000 persons per year for 1971–1972.[29] Appel et al[30] reported a mortality rate of 15.2 per 1000 persons per year for patients in methadone treatment in New York City between 1966 and 1976, mostly for drug-related causes (6.0%) or medical reasons (4.6%). Caplehorn et al[19] found a lower death rate of 5 per 1000 persons per year during treatment; Zanis and Woody[31] reported 4 deaths among 397 patients. Ling et al[32] in their study of buprenorphine treatment found an overall death rate of 9 per 1000 persons per year.

Numbers on mortality in drug dependence may vary for several reasons, including different type of setting and treatment, and different rates of comorbid somatic disorders. In our sample, the rates for HIV (5.9%) or hepatitis C (61,4%) were moderately low compared with other studies.[14] Most studies indicate that patients in methadone treatment die primarily from overdose or HIV/AIDS.[14,33] There is clear evidence that the risk for fatal intoxications is increased during the first days of a maintenance therapy.[7,33–35] As many as 21% of deaths occur within the first 7 days of treatment.[33] Because the patients in the COBRA study were already in treatment for at least 4 weeks, this finding could not be verified in our sample. It has also been consistently reported that the risk of experiencing an overdose is significantly higher for patients who leave substitution treatment compared with those remaining in treatment.[31]

There may also be differences in mortality with respect to different substitution regimens. In our study, the number of deaths in the methadone and buprenorphine groups was relatively equal. Because of its ceiling effect at the opioid receptor,[36] a relatively better safety profile of buprenorphine compared with methadone was recently postulated and supported by French safety data. In France, buprenorphine is far more frequently used than methadone,[37] whereas the number of deaths associated with buprenorphine and methadone are rather equal.[38] Recent data from forensic autopsy material from the upper Bavarian region point into the same direction[39] and indicate a lower rate of fatal intoxications associated with buprenorphine. These findings may be explained by differential use of both drugs. For example, methadone may be more frequently used in patients with higher intensity of dependence or craving. Data from this larger representative sample do not support the previous results from forensic autopsy material. Clinically, there is some evidence for buprenorphine to have less impact on cognitive function compared with methadone[40,41] which may indicate a somehow better safety profile.

The mortality and safety topic deserves further attention. Recently, Schifano et al[42] reported an increase of buprenorphine mortality in the United Kingdom. Interestingly, there was a high rate of suicide verdicts (28%) which we could not find in our sample. When comparing numbers of deaths for different substitution drugs, comorbid drug and alcohol consumption must also be taken into account, as well as the availability of different substitution medications on the ''black market.'' In our study, there were somewhat equal numbers of drug fatalities in both groups.

Clearly, more longitudinal and comparative studies are necessary to study the overdose and mortality risk under different substitution medications and settings. The performance of matching and allocating patients with substance use to different treatment settings and pharmacological regimens remains one of the challenging new topics in the therapy for drug dependence.[27]

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