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- (2) to enhance the provision and quality of services to drug abusers and their families, especially heroin addicts;
- (3) to promote a better understanding of methadone treatment by the general public and its elected representatives and officials;
- (4) to promote collaborative research and to provide a European research centre;
- (5) to work with the American Methadone Treatment Association to promote support for methadone treatment worldwide;
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Mortality among problem drug users in Europe: A project of the European Monitoring Centre for Drugs and Drug Addiction (EMCDD)

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Summary

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is currently co-ordinating a project which aims to enrol and follow up prospective cohorts of problem drug users (PDUs) in several countries, so as to compare overall and cause-specific mortality. Within the project a literature overview of drug user mortality and a comparative analysis of data from already followed-up cohorts were performed. Although the joint analysis provided new knowledge on mortality trends among PDUs in several European countries, care should be taken in comparing data from retrospective cohorts due to the heterogeneity of study populations and their settings and follow-up procedures. The formation of prospective cohorts, in line with a standard methodology, should improve the comparability of results both for overall and cause-specific mortality.

Key words: Drug users - Mortality - EMCDDA - European project

Introduction

Drug abuse is known to have serious health consequences [1, 3, 13-14]. Overall and cause-specific mortality can be considered a valid indicator of the health effects of drug abuse. In most European countries data on drug-related deaths are commonly used in estimating mortality related to substance abuse among the general population and as an indicator to assess the health impact of drug addiction. Many sources of information on drug-related deaths using different criteria for data collection are now available in the

EU countries. Although most European countries have national and/or regional mortality registers, where deaths are coded on the basis of the International Classification of Diseases (ICD), there is a broad heterogeneity of the ICD codes applied to classify “drug-related death”. A specific EMCDDA project has been developed to implement a standard definition and classification of “drug-related deaths” directly linked with the use of drugs (“overdoses” or “poisonings”) in order to improve comparability between countries [4]. However, problem drug users die from a wide spectrum of causes other than overdoses (e.g. AIDS and accidents). Moreover, data on drug-related deaths cannot be referred to a common denominator; they depend on factors such as the prevalence of drug users, and overdose incidence and fatality.

The strength of longitudinal studies lies in their capacity to estimate the current mortality rate among drug users, even if it should be borne in mind that longitudinal studies are carried out on selected groups that may be unrepresentative of the overall drug addict population.

The Agency for Public Health in the Region of Latium (Lazio), Italy, is currently co-ordinating a project promoted by the EMCDDA which aims to calculate and compare mortality rate estimates across a spectrum of European countries through the formation of cohorts of problem drug users participating in enrolment and follow up, in conformity with a common methodology. This paper aims to describe the development of the project and the results already obtained.

Objectives of the project

The broad objective of the EMCDDA project is to promote and co-ordinate the setting up of cohorts of problem drug users recruited through treatment centres in EU Member States, in order to estimate overall and cause-specific mortality rates, while analyzing and comparing longitudinal trends in mortality across countries for monitoring purposes. The project has been developed in the following phases:

- overview of published studies on the mortality of problem drug users that have been undertaken in Europe, and the development of a standardized protocol to assess overall and cause-specific mortality rates among PDUs;
- evaluation of the feasibility of implementing the standardized methodology in various European countries;
- promoting and co-ordinating the formation of cohorts of problem drug users recruited in treatment centres;
- joint analysis of available cohorts.

Results

Review of the literature

A review of the literature, comprising studies and reports/editorials on mortality among drug users in Europe, published between 1980 and 1996, was carried out within the project. The objectives of this overview were to outline the knowledge available on PDU mortality in Europe and assess the comparability of data from different countries.

Of the 33 papers on cohort studies reviewed, 20 were published between 1987 and

1996. Twenty-four longitudinal studies were carried out in European countries. Drug users who had been enrolled at treatment centres in several countries over different time periods showed very high overall and cause-specific mortality rates, ranging from 9.6/1000 in Glasgow in 1985 [7] to 63.8/1000 in Milan in 1991 and 1992 [9]. The main causes of deaths were AIDS and other infectious diseases, overdose, injuries and poisoning, cirrhosis and cardiovascular diseases [2, 5, 7, 10, 16].

All cohort studies showed higher than expected death rates among PDUs compared with a matched general population, although there was variability across study periods, study population and location. The estimated risk of death ranged from 10 to 30 times that of non-drug users of the same sex and age [7, 11, 16]. The excess mortality was estimated almost exclusively among drug users receiving treatment as outpatients. Some studies showed that females have a higher excess mortality than males [2, 11]. Among intravenous drug users, HIV-positive subjects had a higher overall risk of dying than that of HIV-negative ones [6, 8, 15, 17].

The overview of the literature demonstrated that results based on the published data are hard to compare, because of the heterogeneity of the enrolment criteria for drug users, follow-up procedures and methods of data analysis. Most studies have been conducted in eight European countries only, whereas no data were available for the other countries.

Standard protocol to carry out longitudinal studies of mortality among problem drug users

A standard protocol, for carrying out cohort mortality studies among problem drug users, was prepared by defining criteria for the inclusion of subjects in the cohort, follow-up procedures, data collection and methods of analysis. During its development the standard protocol took into account the results of the feasibility study, which was carried out in the early phases of the project. The study aimed to identify subjects to be included in the cohort and to investigate the availability and accessibility of population and mortality registers or similar sources available for determining vital status. The results of the feasibility study showed that the available study population in most countries consisted mainly of addicts entering treatment centres, with some differences both in treatment and in type of substance abused. Using treatment centres as sources of information on study populations seemed the most feasible and reliable option, since identifiers of people enrolled are necessary to assess vital status and cause of death. Moreover, drug addicts who seek treatment are the part of the drug abuse population that has the most urgent problems, and they are not representative of the whole drug user population. In addition, it was considered that at present most PDUs entering treatment in European countries are opiate users. Users of non-opiates (such as cocaine, amphetamines and cannabis) who are admitted to treatment constitute a very special group, and mortality figures derived from this sub-population may be highly biased and unrepresentative of the source population. Opiate users are more likely to enter treatment than other drug addicts, as their health problems are known to be more serious. One outcome is that, in some countries opiate users are the majority of drug addicts in

Table 1. Characteristics of the cohorts					
Study site	Period of enrolment	Study population (N) and setting	Fw-up period	Mean age at enrolment	N of deaths
Sweden	1987-1997	Opiate addicts entering in-patients TCs. Recruitment through the National Hospital Discharge Registry (4023)	1987-1997	30.1	592
Denmark	1996-1999	Opiate addicts entering any kind of treatment. Recruitment through from the National Treatment Database (10355)	1996-1999	31.1	449
Amsterdam	1985-1996	Opiate addicts entering Methadone programs at specialised out-patient TCs and General Practitioners (GPs). Data from Central Methadone Register (CMR) (4853)	1985-1996	29.0	446
Vienna	1987-1998	Opiate addicts in MMTPs at GPs, specialised residential, specialised out-patient, specialised in prison (4683)	1987-1998	27.5	282
Barcelona	1992-1996	Opiate addicts entering out-patient specialised out-patient TCs (4501)	1992-1998	28.6	918
Lisbon	1992-1998	Heroin addicts entering one specialised residential TC and 9 specialised out-patient TCs (2525)	1992-1999	25.3	306
Rome	1980-1995	Opiate addicts entering Public TCs (PTCs) and Non Governmental Organisation (NGOs) (10332). Recruitment through the Local Surveillance System	1980-1996	26.6	1444

treatment. Local and comparative analysis for both opiate and non-opiate users should be carried out where they do not represent a special group.

In the standard protocol included a definition of the study population and the enrolment criteria. All addicts entering treatment at least once during the study period were considered eligible for inclusion in the cohort. As stated in the protocol, the information needed to ascertain vital status must be available and the date of entry at the treatment centre (marking the beginning of the observation period) must be specified, too.

Some essential information was required to provide a description of the people enrolled. This was done to orient the analysis towards enhancing comparability between study sites. Follow-up procedures and their reliability were specified and various analytical strategies were suggested.

Comparative analysis

Although the goal of the EMCDDA mortality project is to describe mortality using a standard methodology, an attempt to analyse and compare data from cohorts that had already been followed up in some study sites was performed. The available study populations appeared to be relatively heterogeneous; they mainly included opiate users, but also comprises variable proportions of users of other drugs (e. g. 24% of amphetamine users in Sweden). To improve the comparability of results, opiate addicts only were included in the analysis.

As shown in table 1, all the analysed cohorts consisted of opiate addicts who had entered treatment, and some differences in period of enrolment, setting and follow up were observed.

The availability of information on individuals enrolled varied across study sites. Gender, age at enrolment and age at death were available at all sites, as well as the variables needed to calculate person-years at risk. The average age at enrolment ranged from 25.7 to 31.1; these were the figures for the cohorts enrolled in Lisbon and in Denmark, respectively.

Figure 1 shows the overall mortality trend in each cohort. The highest mortality rate

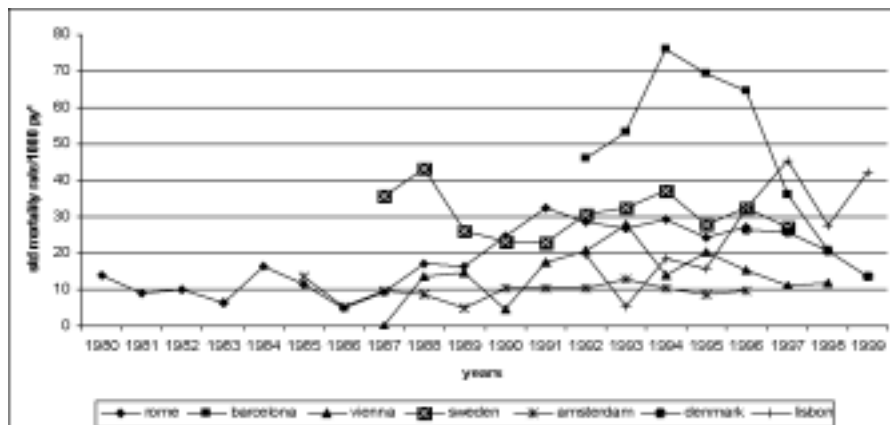


Figure 1. Mortality from all causes: standardized mortality rates (males and females). Directly standardized mortality rates calculated using the European Union population aged between 15-49 as standard. This range was chosen to avoid unstable rates deriving from small numbers of cases per person-years of observation in older age strata.

was observed in Barcelona (75.9/1000 person-years) in 1994 and the lowest in Amsterdam, where mortality rates were consistently below 13.0/1000 person-years over time. In Barcelona a marked decrease in mortality rates in more recent years was reported (20.6/1000 person-years in 1998) – a trend that calls for further analysis. The joint analysis revealed strong differences in overall mortality and trends between study sites, but caution is appropriate when comparing the cohorts retrospectively, due to differences in enrolment criteria, follow up and other variables. In any case, it should be stressed that overall mortality rates have been estimated from cohorts enrolled in various study sites, comprising those countries where longitudinal studies on drug addict mortality had never been carried out before.

Conclusion

There is strong evidence that problem drug users have a higher risk of death than the general population of the same gender and age. The increased risk is only partly due to acute intoxication (overdoses); other causes of death have a strong impact on mortality among drug users. As a result, data on drug-related death and mortality figures estimated through longitudinal studies are useful complementary indicators of the health effects of drug abuse.

The EMCDDA has been working for several years to issue standard guidelines, with the aim of improving the quality and comparability of data on drug-related deaths and of results from mortality cohort studies among PDUs. Eleven European countries (Austria, Denmark, Finland, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden and the Netherlands) are currently collaborating with the EMCDDA cohort mortality project that has been developed, with contributions coming from a group of experts comprising members working in all the participating sites.

The feasibility study and the results of the joint analysis have shown that analysing data from retrospective cohorts is worthwhile in countries where mortality rates have never been estimated, but only as long as access to the required information is easily available. Further analysis is being performed on cause-specific mortality for the cohorts already followed up, and on the possible determinants of mortality.

Most study sites are currently dealing with the enrolment and follow-up of cohorts in line with the standard protocol. The implementation and follow-up of cohorts in conformity with a standard methodology should improve the comparability of results both for overall and for cause-specific mortality. It is, however, necessary to enhance the availability of information on the study population characteristics as required by the protocol.

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Buprenorphine: Evidence for effectiveness

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Summary

In all cases, opiate addiction is best treated by the use of opiate agonist agents. A maintenance regimen based on an opiate agonist leads to a gradual dwindling of the subjective effects due to street opiates, thanks to the blockade achieved by these agents on the receptors that are reached by heroin.

Buprenorphine looms as the most useful of the latest generation of agonist agents for the treatment of opioid use disorders. It is equivalent to other opiates as regards retention rates and control of street opiate use. Apart from maintenance programmes for opiate addiction, buprenorphine has proved effective in short-term programmes for opiate detoxification.

Buprenorphine treatment should be regarded as first-line in subjects with low levels of craving and low severity of addictive behaviours, as long as: 1) it is documented that low methadone doses produced complete and stable remission; or 2) after a period of ongoing abstinence in drug-free conditions, the patient has recently relapsed into use of street opiates, so that their tolerance threshold is presumably still low. For subjects, whose tolerance is unknown, or when anamnestic or objective elements suggest there may be a high tolerance threshold, or else in cases comprising a recent history of unresponsiveness to low dose methadone treatments (below 60 mg), methadone should be the first choice for the therapy of opiate addiction. Subjects who have proved to be refractory to buprenorphine, even at higher dosages, can reasonably be directed to a methadone treatment programme.

Key words: Buprenorphine effectiveness - Opiate abuse - Predictors of outcome - Cocaine use - As antidepressant - Opiate withdrawal

In all cases, opiate addiction is best treated by the use of opiate agonist agents. This therapy calls for the administration of constant doses of an opiate agonist at constant time intervals, over a period of months or years. Historically, methadone and LAAM are the main agents that have achieved success in treating opiate addiction in therapeutical settings. A maintenance regimens based on an opiate agonist leads to gradual dwindling

of the subjective effects due to street opiates, thanks to the blockade achieved by these agents on the receptors affected by heroin. The vicious circle between intoxication and withdrawal which is bound to develop in heroin addicts, and which marks the revolving-door stage of their addictive careers, is itself showed and then broken. Agonist-maintained subjects display a satisfactory retention rate, have their neuroendocrine functions restored, from a condition of imbalance due to chronic opiate intoxication, and are kept off addictive behaviours (crime, spreading of HIV, pregnancy accidents). On this basis, former addicts are able to benefit most from concurrent psychosocial support facilities. On the whole, it can be stated that agonist maintenance effectively forestalls criminal behaviours, the abuse of street opiates and the risk of transmitting infective diseases, while guaranteeing quite a high retention rate.

Buprenorphine looms as the most useful of the latest generation of agonist agents for the treatment of opioid use disorders. It displays a unique pharmacological profile, which makes it suitable for various treatment strategies: in fact, it possesses a high binding-affinity for μ and κ receptors, by acting as a partial agonist for μ receptors and as an antagonist for κ receptors. Several studies provide evidence of its effectiveness on heroin abuse/dependence. On practical grounds, the usefulness of buprenorphine's properties can be described from a variety of viewpoints. It is equivalent to other opiates as regards retention rates and the limitation of street opiate use. Administration can take place daily or three times a week. Tolerability is acceptable. An optimization of buprenorphine's efficacy should be based on the identification of positive and negative predictors, to be used later as selection criteria for patients whose chances of responding positively may differ widely. Apart from maintenance programmes for opiate addiction, buprenorphine has proved effective in short-term programmes for opiate detoxification. Moreover, it has been indicated as probably being effective in cocaine abuse/dependence and as an antidepressant drug for refractory depression.

The present study aims to present a critical review of the buprenorphine-related issues outlined above.

Opiate abuse/addiction

Effectiveness in opiate abuse

Within a dose range of 2-32 mg, buprenorphine has proved as effective in controlling opiate use at low methadone doses (20-60 mg), with an equivalence relationship to be read as mirroring the corresponding μ -opioidergic activity. Some time ago, its level of effectiveness was established on clinical grounds, by monitoring the level of its anti-withdrawal and anti-craving activity. More recently, the potency of these two agonists has been investigated by brain-imaging techniques, in terms of their respective rates of μ -receptor occupation. These accounted for buprenorphine's greater affinity and methadone's higher potency. These two ways of defining dose-adequacy are in agreement: in other words, the effectiveness of buprenorphine at a certain dose is equal to that of methadone because it provides the same level of μ -receptor stimulation [9; 30].

After accounting for the percentage of negative urinalysis, 8 mg of buprenorphine

are superior to 20 mg, but equal to 50/60 mg of methadone [11]. In addition, when patients are chosen so that their tolerance threshold is the same (by a pre-treatment evaluation based on a naloxone-challenge) [11], the superiority of buprenorphine may clearly be ascribed to its anticraving activity, rather than its anti-withdrawal effect. Otherwise, subjects treated with either of these two agonists at lower equivalent doses, but who are less tolerant at the beginning, show a poorer response. Moreover, after stabilization has been reached (i.e. within about four weeks) possible relapses into the use of street opiates, which are more likely than with low-dose methadone, cannot be justified on the grounds of persistent withdrawal symptomatology [11].

80 mg of methadone, which cannot be equalled by any buprenorphine dose, are superior to 8 mg of buprenorphine [17] – a dose that corresponds to about 50/60 mg of methadone. Likewise, craving is better controlled by 80 mg of methadone [17]. Even if higher buprenorphine doses were administered, no consistent gain in agonist activity would follow, due to the plateau reached on the dose-effect curve after an eight mg dose-level (known as the “ceiling effect”). One study has reported the equivalence, on clinical grounds, of 8-16 mg of buprenorphine and 50-90 mg of methadone, but it should be noted that the average doses administered are 9 mg and 54 mg, respectively, so that in the last analysis equivalence comes to stand for m-equipotent doses [28].

From the standpoint of ensuring a stable condition of abstinence, data from the literature do not agree in indicating a superiority of buprenorphine to equipotent methadone doses [11; 26]. The efficacy of treatment, when doses are kept stable, does not seem to vary through time, while an increase in doses results in efficacy enhancement [26].

Even if the final outcome is the same, methadone offers quicker progress to adjustment, (first month) [18], whereas the efficacy of buprenorphine builds up gradually. The fact that buprenorphine is characterized by a therapeutic gain which is progressive in the medium-term [28], though not wholly superior at the end of observation, does suggest that buprenorphine allows a satisfactory outcome in the medium-term, despite lower effectiveness in the early stages (as shown by rather high rates of early dropout) [19]. This property is dose-dependent, and probably reflects that combined blocking property (so-called antagonism) which favours the conditions needed for abstinence to begin. Although high methadone doses provide a blocking effect (80-120 mg), heroin reinforcement can usually be elicited at buprenorphine-equivalent doses of 20-60 mg.

Gradual dose-reduction worsens the opiate-use status [26], probably due to craving shooting up, since severe withdrawal symptoms during medically supervised tapering are very unlikely [20]. High buprenorphine doses are linked with a better outcome than lower doses, with a threshold as high as 8 mg for a satisfactory response. Some subjects, however, show a satisfactory outcome with lower doses: in a 16 week follow-up study, differences emerging from the use of high versus low doses during the early weeks tend to fade towards the end of the study [17]. At a 16 week term, 8 mg have the same effect as 1 mg; after 8 weeks 4 mg are no longer superior to 1; at 12 weeks, 16 mg are as effective as 1. This means that, amongst patients who are retained in treatment, there is

a subpopulation that responds to low doses. Other studies have, in fact, reported a good level of efficacy for 2-4 mg or 2-6 mg [13; 25]. In general addict populations, however, buprenorphine efficacy is dose-dependent, both in the whole sample, and in the responding subgroup [16].

Retention in treatment

Treatment retention, when calculated as the proportion of patients who stay in treatment at a certain term, can be read as an indirect index of effectiveness. This depends on the fact that retaining a patient in treatment makes it possible to achieve stabilization if the period is long enough; that is the main objective, along with the need to maintain the achieved results as long as possible. When doses remain unchanged, treatment duration provides no further benefit in terms of craving reduction, though longer treatments mean a lower risk of relapse when a patient is left drug-free. Retention does allow the resumption of psychosocial adaptation, which is a gradual process requiring stability over quite a long time, and develops alongside the maintenance of acquired abstinence. Buprenorphine has turned out to be an exception to this scheme, due to its combined agonist-antagonist properties at doses equipotent to 20-60 mg of methadone. If heroin use persists during buprenorphine administration, virtuous circle involving negative reinforcement can develop, so further decreasing opiate use through time, in association with expected social rehabilitation. An eight mg threshold seems to be definable for this phenomenon [18], corresponding to the threshold for a consistent receptor blockade. In general addict populations, however, a higher level of agonism than that made available by buprenorphine – as high as that provided by 80 mg of methadone – corresponds to a higher level of efficacy on craving, both in the short and long term. Retention in treatment with 8 mg of buprenorphine is comparable with that of equipotent doses of methadone [18] in the short term (4-6 mos). In only one study [12] a high early retention rate (72%) was documented for relatively low doses (2-6 mg), whereas most findings show agreement in describing the drop-out phenomenon with buprenorphine as coming earlier and as being more likely with low doses. Early retention does not relate to dosage, but a correlation is found with the degree of withdrawal symptoms [27]. We suggest this means that early retention depends on the effectiveness of treatment in suppressing withdrawal discomfort, which is not linked with dose as such, but with the adequacy of dose to the patient's tolerance threshold. In fact, other authors [27] reported a lack of correlation between agonist dose and retention, whatever the agonist, and, conversely, the importance of withdrawal control. High doses of buprenorphine bear a higher likelihood of retention than lower doses, around a threshold of 8 mg [16]. Isolated observations suggest a weaker effect on retention during the first weeks of treatment, along with the inadequacy of buprenorphine in cases with moderate-to-high tolerance levels. On the other hand, when subjects are directed to buprenorphine or methadone according to their level of tolerance, early retention with 8 mg of buprenorphine is even higher than with 60 mg of methadone [11]. A lack of differences in late retention between methadone and buprenorphine has been documented,

as far as equipotent doses are concerned [11]. Higher doses result in a greater likelihood of retention [17]. Recent results from a long-term high-dose maintenance study [5] document a 70% rate of retention at a two-year term, with 1.2% of successful completion of the programme. The absence of a massive early drop-out in this sample may be due to its being composed of heroin-addicts who were spontaneously asking their GP for treatment [27]. This justifies the supposition that they were a special subpopulation characterized by psychosocial adjustment and low severity of disease, that is, the category of patients who would be expected to benefit most from buprenorphine maintenance.

Daily vs. three times a week administration

When patients are started on buprenorphine, intermittent administration causes withdrawal symptoms to emerge within the 24-hr time windows between administrations. This phenomenon can easily be explained in terms of the inadequacy of the stimulation provided by buprenorphine against high tolerance thresholds, especially when blood levels tend to fall within a 24 hr time frame, as happens before a steady state is reached. A wider gap between maximum and minimum blood levels is recorded when buprenorphine is administered less often; in that case withdrawal symptoms display a consequent intermittent course towards extinction, which is only reached gradually [11]. Likewise, as far as maintenance is concerned, the intermittent administration of as much as 16 mg every second day may be associated with mild withdrawal-like symptoms during “free days”, or may show no difference from the corresponding daily administration schedule [10]. When doses twice as high as this (32 mg/two days) are used, minor withdrawal annoyance was not observed [23].

Safety and tolerability

It can be stated that buprenorphine is mostly well-tolerated. Reported side effects appear during the induction phase and include sedation/drowsiness/giddiness [14], general discomfort (dizziness), dysphoria, nausea and headache. As long as such effects are tolerable and do not lead to drug discontinuation, they are likely to have dwindled by the time of stabilization. To favour early retention during the induction phase, it is advisable to temporarily stop administration during the next 24 hrs, when signs of opioid overstimulation, such as nausea, headache, sedation and constipation, may appear. No increase of dose is recommended before the above symptoms have disappeared. The number of side effects attributable to buprenorphine from 1st November, 1997 to 1st November, 2000, using FDA data, are 178, versus 170 for methadone and only 40 for LAAM. Considering that, so far, many fewer subjects have been started on buprenorphine, compared with the almost 450,000 on methadone and 10,000 on LAAM, the incidence of side-effects could loom rather large [15]. Buprenorphine overdosing is, however, very unlikely [15]. From 1994 to 1998, the overdose rate among 55,000 French buprenorphine-treated subjects was three times lower than that among 5,360 methadone-treated patients [1].

Predictors of outcome: towards an optimal targeting

Apart from the evaluation of tolerance threshold and intensity of craving, the choice between methadone and buprenorphine should be based on the assessment of specific outcome predictors. Cases of negative outcome with buprenorphine treatment tend to be characterized by more severe psychosocial maladjustment at the beginning of programmes [21]. When a maintenance programme with 8 mg of buprenorphine was compared with one employing 60 mg of methadone, predictors of negative outcome at a six-month term can be identified for buprenorphine-treated subjects that are not valid for methadone maintained probands: severe psychosocial maladjustment, high levels of craving for cocaine, and a high degree of psychopathology, especially of a depressive and paranoid kind. Conversely, no prognostic weight of baseline depressive symptomatology is reported for 4 mg-treated subjects. The contrast between the data might be explained by the fact that, when lower agonist doses (4 mg) are used, treatment failure is mostly due to its ineffectiveness on craving or withdrawal symptoms, whereas in higher dose programmes (8 mg), a positive response is likely except with mentally ill or severely maladjusted addicts, who tend to cluster among non-responders. Female gender has been also reported to favourably condition responses to buprenorphine, when 4 mg are compared with 20 or 65 mg of methadone [24]. Authors suggest that the difference is related to the documented higher analgesic sensitivity of women challenged with κ -opioid-agonists [7].

The optimum management of buprenorphine should therefore be based upon the selective enrolment of subjects displaying the following: psychosocial adjustment, absence of major psychiatric illness, especially of a depressive and paranoid quality, and low severity of addiction, as shown by a low tolerance threshold and a low level of craving. Concurrent cocaine use, despite suggestions about the possible effectiveness of buprenorphine in this matter, should represent a reason to direct patients to methadone maintenance. As a result, the selection criteria for buprenorphine treatment are intermediate between those of antagonist treatments, which fit cases of mild disease only, and full-agonist treatments, which fit any gravity of disease, including several cases of dual diagnosis.

Buprenorphine as short-term treatment for opiate tolerant individuals (detoxification by buprenorphine)

Buprenorphine is, predictably, as effective in detoxifying heroin addicts [2] as methadone, when μ -equivalent doses are used. When compared with clonidine, it has proved to be less effective on tremors and on rising blood pressure, and it takes longer to control withdrawal symptoms as a whole. However, the longer latency for an anti-withdrawal efficacy is counterbalanced, after the first 24-48 hrs, by a more consistent healing pattern, and a greater impact on psychopathological items [4]. An apathetic-asthenic-abulic syndrome, which can develop with clonidine, is not found with buprenorphine administration. When withdrawal is due to the discontinuation of a long-

lasting agonist agent (e.g. methadone), and that agent is not available to be reintroduced and then tapered, buprenorphine should be preferred to any non-opiate chemical, since withdrawal from a long-lasting opiate does not require early buffering (which is needed in the case of rapid morphine-like opiates), but long-term buffering, though results are best if this starts soon after withdrawal. So treatment should begin as soon as withdrawal symptoms appear, but no earlier, in order not to elicit them as full-blown, and dosage should be increased in line with the patient's response.

During detoxification, it is fundamental to achieve discontinuation of street opiate usage, or at least to have possible street opiates made ineffective, so that tolerance is not kept high, and agonist doses can be tapered without any major withdrawal discomfort. This objective, which is granted by hospitalization, is uncertain when addicts undergo detoxification as outpatients. Buprenorphine may prove particularly useful in this context, due to its combined agonist-antagonist properties, at least at doses above 8 mg. It has been documented that 2 mg are less effective than 30 mg of methadone at blocking the effects of heroin [2]. It may therefore be suggested that a significant difference between receptor blockade with buprenorphine or with methadone, at equipotent doses, only emerges beyond an 8 mg dose threshold of buprenorphine. As regards frequency of administration, buprenorphine should not be administered less often than once a day in a detoxification regimen [6].

Buprenorphine and cocaine use

Buprenorphine's rate of effectiveness is negatively affected by concomitant cocaine use: when buprenorphine, at a dose of 8 mg, was tested, treatment retention for a general population of heroin addicts, where the frequency of cocaine use was as high as 66%, was lower than in a group of subjects selected to ensure the absence of concurrent cocaine use [18] (78% by 12 wks vs. 50% by 17 wks). While opiate usage tends to dwindle as buprenorphine doses increase, cocaine usage shows no such a trend [27]. The relationship between cocaine use and buprenorphine dose is not constant, but varies according to buprenorphine dose. 2 mg of buprenorphine enhances the pleasurable effects of cocaine, along with the faster heart beat that follows cocaine intake [22]. Doses of 4-8 mg do not block or enhance the same effects, and they leave cocaine highly distinguishable [29], as it is in natural conditions. For addicts maintained on 8 mg of buprenorphine, a higher baseline craving for cocaine is predictive of a drop-out outcome, whereas no increase in cocaine-related likelihood of drop-out is displayed by subjects treated with equipotent doses of methadone [19]. Recently, disulfiram has proved to be rather effective when targeted at cocaine-abusing heroin addicts as an add-on therapy to successful buprenorphine maintenance [8]. As no evidence of a toxic interaction between buprenorphine and cocaine has been documented so far, the safe use of buprenorphine for the treatment of heroin addiction can be viewed as feasible, even when cocaine use is concurrent. On the other hand, no data from the literature suggest there may be a specific effect of buprenorphine on cocaine use.

Antidepressant properties of buprenorphine

In heroin addicts, depressive symptoms may develop either as a result of opiate agonist undermedication, or a residual after detoxification, for individuals who are kept abstinent in a drug-free condition or on antagonist maintenance. Besides, depression may also appear during the maintenance phase of an opiate agonist treatment programme. In that case, it has not yet been assessed whether buprenorphine provides any specific benefits compared with those given by equipotent methadone dosages. However, when methadone doses are tapered down to a dose-range low enough to allow transition to equipotent buprenorphine treatment, this leads to the emergence of a depressive symptomatology due to current undermedication, besides which there is the risk of relapse into opiate addiction. Even when full-blown withdrawal symptoms are not elicited, a lowering of opioid stimulation matches with emerging symptoms of psychasthenia, which display a chronic course (delayed withdrawal). Kosten [12] reported the usefulness of buprenorphine in depressed patients in whom depression had developed along the tapering phase of a short-term agonist detoxification (from an average peak of 55 mg/die, down to 25 mg/die, with later transition, after a two-week stabilization interval, to buprenorphine, 3.2 mg/day on average). The therapeutic gain was worthwhile and came early (within the first week), but no evidence is available yet to justify the application of these results to the issue of depression in heroin addicts, let alone to depressive syndromes in the general populations, since this particular sample consisted of previously agonist-stabilized subjects who were later likely to experience a condition of undermedication.

While depression was assessed before subjects were started on buprenorphine, that is after preliminary methadone tapering, no information was gathered on the occurrence rate of depressive symptoms at study entrance, that is, during previous higher dose methadone treatment. Moreover, successful treatment with 55 mg/day average methadone dosages characterizes a low-craving subpopulation with moderate to low withdrawal thresholds, since standard methadone dosages capable both of controlling withdrawal phenomena and the craving for opiates have been reported to stand much higher, within a range of 80 to 120 mg/day. It should be also noted that the inadequacy of buprenorphine in buffering depressive symptoms as they emerge may not affect retention in treatment, at least as long as the soothing of early withdrawal symptoms – the feature that addicts are most concerned about – is guaranteed. Elsewhere, it has been reported that drop-out rates from buprenorphine treatments tend to turn higher for more depressed probands [19], while depressed heroin addicts fail to show greater benefits from buprenorphine treatment than from methadone treatment [21].

Ten non-addicted depressed patients, diagnosed as affected by Double Depression (Major Depressive Episode occurring against a background of dysthymia), mostly with atypical features, who had proved to be refractory to standard antidepressant agents, were quite responsive to buprenorphine, with a therapeutic gain displayed most strongly during the first week of treatment [3], in line with what Kosten reported for depressed heroin addicts [12]. It must, however, be noted that substance use disorders were present in this small sample, as well as comorbid anxiety disorders.

Buprenorphine for the treatment of opiate withdrawal

When opiate withdrawal is to be treated in subjects whose tolerance threshold has not been ascertained, two practical rules should be followed: 1) using an agonist agent, start with low doses, so as to avoid overdosing in opiate-sensitive individuals; 2) choose an agent with such a dynamic profile as to be effective, by dose variation, within as wide a range of stimulating levels as possible, in order to ensure a feasibly high tolerance condition with adequate buffering. Anamnestic information about quantities of substance consumed, and time since latest intake, might be useful in estimating the tolerance threshold, so allowing the selection of subjects who, due to a moderate-to-low tolerance threshold, are likely to respond to low methadone doses, and, therefore, to equipotent buprenorphine treatment. Even so, considering methadone's wide range of agonist potency, it should be the first choice in the treatment of withdrawal states, unless these are due to the withdrawal of buprenorphine. Moreover, though buprenorphine's partial agonism precludes the risk of overdosing, when high dose buprenorphine is found to be insufficient to control high threshold withdrawal, the successive administration of a full agonist is likely to be awkward: due to the high binding affinity of buprenorphine to μ -receptors, and its long half-life, buprenorphine displacement requires high doses of lower affinity full agonists, with a delayed risk of overdose as the buprenorphine level is reduced. Lastly, when buprenorphine is administered to highly tolerant addicts displaying initial withdrawal symptoms, with heroin levels still high enough to delay full-blown withdrawal, this latter may be precipitated due to displacement of heroin from μ -receptors by stickier buprenorphine.

The role of buprenorphine in the treatment of opiate use disorders

Buprenorphine treatment should be regarded as first-line in subjects with low levels of craving and low severity of addictive behaviors, as long as 1) it is documented that low methadone doses produced complete and stable remission; or 2) after a period of ongoing abstinence in drug-free conditions, the patient has recently relapsed into the use of street-opiates, so that their tolerance threshold is presumably still low. Moreover, the use of buprenorphine is indicated in the early phase of addiction, when tolerance is still low and craving levels have not yet peaked, so as to prevent craving from shooting up and the metabolic phase of addiction from being entered. During the "honeymoon" phase, as long as the patient is compliant, the antagonist property of buprenorphine may prove useful in moving them off heroin, in addition to the effect of its main anticraving action.

For subjects whose tolerance is unknown, or when anamnestic or objective elements point to a high tolerance threshold, or those with a recent history of unresponsiveness to low dose methadone treatments (below 60 mg), methadone should be the first choice for the therapy of opiate addiction. Subjects who have proven refractory to buprenorphine, even at higher dosages, can reasonably be directed to methadone treatment programmes. Buprenorphine, therefore, represents a possible

first-line agent instead of methadone, for subjects who display clinical features that make it likely that they will respond to low methadone doses (below 60 mg). This category of subjects, who can be enrolled in buprenorphine treatment programmes, may represent a self-medicating subpopulation of heroin addicts, who need low opiate doses and therefore develop low tolerance. Whether buprenorphine is preferable to methadone because of specific psychotropic properties is still a matter for research.

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1995-2001 programme evaluation of the A-center for treatment of addicts consuming prohibited drugs at Maribor, Slovenia

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Summary

A study covering six years of treatment at our centre was dedicated to 570 patients addicted to prohibited (because illegal) drugs; those patients were enrolled in the period April 1995 - April 2001. Group A results are those for 284 addicts treated with methadone, while those for group B refer to the comprehensive treatment outcomes for all 570 addicts enrolled there in that period. Patients in group A had an average age of 26 years, and an average daily methadone dose of 80 mg, the following infections were recorded: (i) 21 patients (7.4%) had the hepatitis B virus, (ii) 105 (36.9%) had the hepatitis C virus, and (iii) no patients (0%) had the HIV virus. For 16 patients (5.6%) the results are unknown.

Analysis of the cause of death within this population shows approximately the same percentage (1.4%) for each of the four items: suicide, overdose, violent death and traffic accident. In April 2001 164 addicts were being treated in the methadone maintenance programme (VMP). In the larger group, B (n=570, all the addicts treated), the average age was 24 years, with percentages for infection with HBV, MCV and HIV below those for addicts in VMP. For 109 patients (19%), the results are unknown. Comorbidity was frequent; it involved 178 of these patients (37%): 115 patients were diagnosed as having personality problems (20%) and 58 (10%) as having endogenous psychic diseases.

Key words: Evaluation of treatment results - Methadone Maintenance Programme - Comorbidity of addicts - Extent of HBV, HCV HIV infection amongst addicts

Introduction

The Maribor centre is one of five A centres in the Republic of Slovenia, whose objective is to treat addiction to prohibited drugs. There are also a number of B centres, which are associated with these A centres. The institution that coordinates all the

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addiction treatment programmes in the republic is the detoxication centre in Ljubljana, which acts as part of the Clinical Department for Mental Health at UKC (University Clinical Centre).

The activities of our centre, which has been open since April 2, 1995, are as follows:

- addiction diagnostics
- preparation for treatment
- individual treatment
- collective treatment, taking place once a week
- a joint review of the therapists' work, held twice a month
- cooperation between the coordination bodies in Ljubljana and Maribor
- assistance with the psycho-social rehabilitation of addicts
- assistance given to the B centres in Murska Sobota
- medical services to addicts for the day centres known as "Maribor - Healthy Town"
- substitution and maintenance methadone programme
- complete management of the laboratory diagnostics of addicts
- vaccinations of addicts against hepatitis A and B
- permanent education
- permanent presence in the public media of our town
- lecture programmes in schools and participation at round tables
- passive and active participation at international congresses
- preventive work with young people (in Croatia and in Italy).

A brief presentation of the rules of the Substitution and Maintenance Methadone Programme (VMP) in Slovenia.

This programme is reserved for patients under 18 who have failed to complete two or three (documented) treatments of addiction and have proved to have taken hard drugs (heroin) intravenously for a period of at least a year.

Other criteria for admission include several laboratory findings (e.g. testing positive to opiates), and auto- and hetero-anamneses. Pregnant addicts, who are unable to live without illegal drugs, are also entitled to this programme, as well as addicts infected by the HIV virus – fortunately, no addicts have tested positive in Slovenia, so far. Methadone is distributed every day from 7 a.m. to 2 p.m., dissolved in fruit juice, which the addicts have to drink in the dispensary in the presence of our medical staff. In special cases (stable, settled and employed clients) exceptions are permitted.

Group work takes place in the afternoons; each of four groups is led by one therapist. Two of them comprise two co-therapists. At the moment all the group work, including that involving the therapists, is supervised and/or peervised by the centre head. Over the past four years 250 addicts have been vaccinated against hepatitis A or B (3x). In the six years following the opening of our centre (April 1995 to April 2001) 570 addicts were treated there. If it is borne in mind that only 10 to 15% of these

patients received medical treatment, it is easy to form an epidemiologic picture of the addiction to prohibited drugs in Maribor, which has a population of about 200,000 inhabitants.

In those six years 284 addicts attended the methadone programme; of these, 164 were still receiving treatment in April 2001. 286 addicts are included in our full range of programmes – in the detoxication centres, in the communities of Don Pierino, Patriarče and Syanon, in the hospital or at the day centre known as “Maribor - Healthy Town”. The trends for initial examinations still show no increase in number of applications. The programme at our centre is a low-threshold one, which means that we try to offer help to every addict who asks for it. Of course, many addicts are unable to fulfil even the minimum requirements, so there is a considerable drop-out rate from the programme.

A higher threshold level for the work in the centre is attained by the meetings with groups of parents and addicts. In this case the results are better and more stimulating than with individual methadone treatment.

Report

GROUP A: This comprises 284 addicts, who in the period April 1995 - April 2001 were treated in the methadone maintenance programme (VMP). In April 2001 164 of these were still being treated in VMP. The daily dose of methadone was 80 mg, the average age was 26 years and the ratio between male and female patients was 2.6/1 (208/76). 21 patients (7.4%) were infected with HBV, 105 (36.9%) were infected with HCV and none were infected with HIV. The percentage of unknown results is 5.6% (16 patients).

The review of cause of death gives the following outcome: 3 deaths from suicide, 4 from an overdose, 2 from a traffic accident, 2 from an illness and in 4 cases addicts were the victims of violent acts. 53 patients (about 10%) were prosecuted and/or punished. Comorbidity was diagnosed for 107 addicts (38%), 63 of whom had personality problems (22%), while 45 suffered from psychotic diseases (16%).

GROUP B: In this group the results for all the patients treated at the centre were considered globally (for the period April 1995 - April 2001), so that this group comprised not only VMP but also the dispensary approach, the pre- and post-hospital treatment, psycho-social rehabilitation, and so on. The average age was 24 years, and the ratio between male and female patients was 2.9/1 (427/143).

None of the group were infected with HIV; 21 (3.7%) were infected with HBC and 116 (20.3%) were infected with HCV. The percentage of unknown results (many treated patients were not willing to take all the required tests) was 19% (109 patients). In the 6-year period, 24 people died (4.2%). Of these, 5 (less than 1% of group B) committed suicide, 10 (1.7%) had taken an overdose, 5 were murdered and 4 were victims of traffic accidents (2%) or an illness (2%). Comorbidity was diagnosed for 178 addicts (31%),

of whom 115 had personality problems (20%) and 58 (10%) endogenous psychosis.

The results of the therapeutic treatment are as follows:

164 addicts (28%) were retained in VMP, 47 (8.2%) went to communities, and 50 (8.8%) were treated in hospital. In spite of receiving all kinds of help, about 45% (256) continued to consume prohibited psychoactive substances (PAS), whereas 10% (57 patients) became PAS-free.

Comment

In this section the data for 1997 will be compared with those presented so far (for 2001). The results of 6 years of work with addicts on prohibited PAS in Maribor show that the number of patients on the methadone maintenance programme is rising, as is the total number of all addicts treated. Five years ago (1997) the ratio between male and female patients was 3.4/1, whereas it was 2.9/1 in 2001. In addition, the average age of addicts has fallen from 24.8 to 24 years.

By comparison with 1997, the percentage of those infected with HCV was almost 13% lower in 2001, while the percentage of HBV infection was unchanged. The results show the effectiveness of low-threshold programmes (condomats, needle-exchange programmes and health prevention), besides, of course, the importance of keeping the addict population well-informed and aware of the dangers of these infections.

One encouraging fact is that none of the addicts on prohibited drugs (PAS) tested positive to HIV infection. In 1997 the percentage of unknown results was 26%; in 2001 it was “only” 19%.

In 1997 the average dose of methadone was 65 mg, in 2001 it was 80 mg. The drop-out from VMP was smaller. When comparing the number of those dying in the years between 1997 and 2001 a significant increase can be noticed, from 3.7 to 4.3%. The increase is mainly the result of violent behaviour and overdoses.

The problem of comorbidity has not changed significantly. In both the two periods being compared, it amounted to approximately one third of all the patients being treated.

Again, the percentages for therapeutic successes and failures were similar. In both periods one third to one quarter of the addicts were retained, about 10% go to communities and a similar percentage become drug-free. 45% continue to consume prohibited PAS.

In working with addicts supporting therapy is important, as well as the education of addicts and their relations or partners, group work with them and psychosocial support.

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Does therapeutic threshold of methadone concentration in plasma exist?

**Lubomir Okruhlica¹, Ferdinand Devinsk², Jindra Valentova²,
Danica Klempova²**

Summary

This study was conducted among the group of 69 patients in the methadone maintenance programme in Bratislava. There were 56 males and 13 females, with an average age of 26.9 years (SD 5.4). Daily methadone doses (mean: 134 mg, SD 56.1, from 10 to 270 mg) were compared with methadone concentrations in plasma (mean: 376.6 ng/ml, SD 226.1, from 44 to 1103 ng/ml); of these, 17.4% of the patients had levels below the threshold of 200 ng/ml of plasmatic concentration of methadone, whereas 15.9% had levels above the level of 600 ng/ml. All of them had previously been stabilized clinically, with negative urinalysis for morphine.

Key words: Methadone - Plasma Concentration - Maintenance Therapy - Methadone Dose

Introduction

On the programme level there are two main indicators of the treatment effectiveness of maintenance programmes: (1) retention rate of the patients in it and (2) the proportion of negative/positive urinalysis for morphine [20, 21, 9, 19, 22, 1]. On the individual level the main clinical criteria for an appropriate methadone dose are: (1) no signs of withdrawal state, (2) no craving for use of opiates, (3) no illicit opiate use [12, 18].

Evaluation studies have brought considerable evidence that, with an increase in average methadone dose for those in the programme, there is lower drop-out and a lower proportion of urine tested positive for morphine [5, 2, 22, 23, 18]. The "ASAM Board of Directors' Issued Statement on Public Policy on Methadone Treatment" (April 1990), states, inter alia, that: "Determination of methadone dosage by program policy

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is inappropriate. Dosage should be individually determined by well-trained clinicians based on subjective and objective data and be adequate for the individual patient in all cases". The benefits of individualized methadone dosing are well documented [17].

The implementation criteria for objective clinical signs of withdrawal and the history of illicit opiate use for dose management without upper dose limitations, led some clinicians to prescribe doses up to 780 mg per day or even higher [18]. A high degree of inter-individual variation was found in the doses prescribed for single patients. Some of the research carried out has attempted to explore these differences by studying methadone plasma levels. Several studies have aimed to find a minimum methadone blood level which can reliably support effective methadone maintenance therapy. Some of the studies reported no such threshold [3, 25, 7], while the others put forward a range of values, between 50 and 600 ng/ml [10, 24, 4, 6, 11, 16, 15, 26]. Loimer and colleagues [14] suggest that methadone plasma concentrations of 400 ng/ml are necessary to suppress any further opiate action and provide stable maintenance.

Using these modern criteria for each patient's individual dose assessment, we have confirmed wide variations in the individual daily doses prescribed for patients in our methadone maintenance programme in Bratislava. The main goal of this study was to find out whether we would be able to determine a threshold for methadone plasma level and, if so, with what accuracy.

Material and Method

The methadone maintenance programme in Bratislava, from which the study sample was chosen, has an overall retention rate of 84% 12 months into the programme. There was a proportion of 13% urine randomly tested positive for morphine in last 2.5 years. The programme is a complex one, comprising group therapy, a cognitive-behavioural approach and contingency management. Methadone hydrochloride in liquid form is dispensed under medical staff supervision, after being mixed with juice, at a methadone out-patient clinic. Take-homes are allowed for week-ends. Recently the patients were also allowed to collect methadone twice a week, but only if they had been doing well in the programme for over one year.

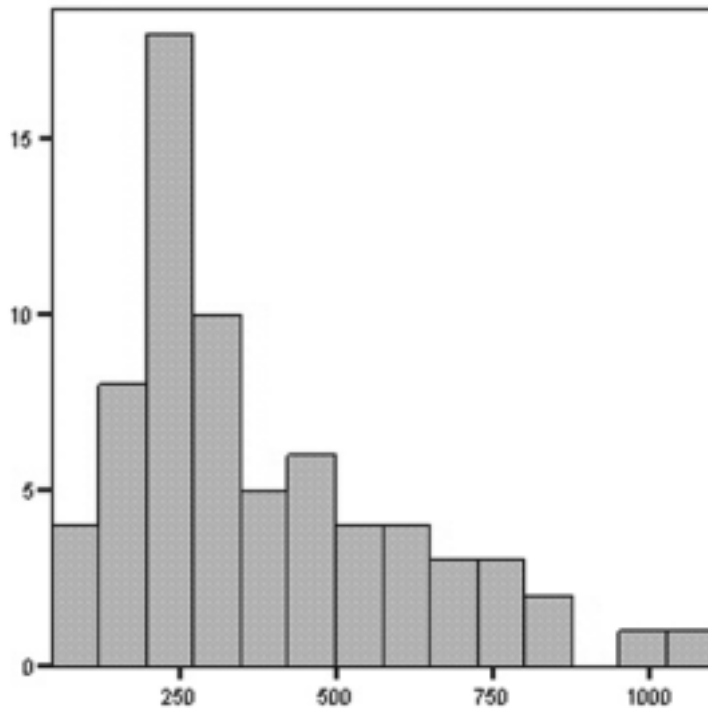
The study group was formed of 69 patients from the methadone maintenance programme, with an average age of 26.9 years (SD + 5.4; median 26). 56 (81%) were males and 13 females (19%). Their average daily methadone dose was 134 mg (SD 56.1), with a range from 10 mg to 270 mg. Collection of blood for methadone plasma level testing was conducted during regular assessment of their condition after completion of one year in treatment. All of them were under close staff supervision when drinking their daily dose at the clinic four days prior to blood taking. The blood was taken for assessment through plasma level from 23 to 25 hrs after their previous dose of methadone, usually on a Thursday. None of the patients had positive urinalysis for morphine on that day. All of them were well stabilized. They had had negative urine for morphine at least for the previous month, but in most cases much longer. Quantitative

analysis of blood samples for methadone was performed in an analytical laboratory, where GC/MS methodology was used. SPSS statistical software was used for data analysis.

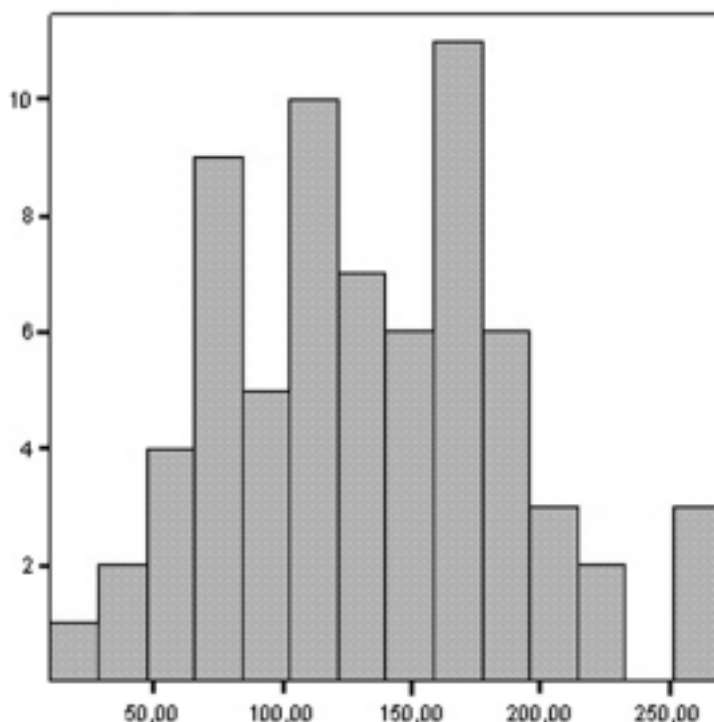
Results

Detected average concentration of methadone in plasma was 376.6 ng/ml (SD 226.1; median 307 ng/ml) in a range from 44 to 1103 ng/ml. Distribution of the frequencies of different plasma concentrations are shown by histograms (Graph 1). Distribution of the frequencies of different doses of methadone appears in Graph 2. A scatter plot diagram demonstrates correlation between dose and methadone level in plasma (Graph 3). When we applied a minimum threshold of 200 ng/ml and a maximum limit of 600 ng/ml of through-plasma methadone concentration on our sample, we detected that 12 (17.4%) patients had plasma levels below the threshold and 11 (15.9%) above the upper limit.

Graph 1.



Graph 2.

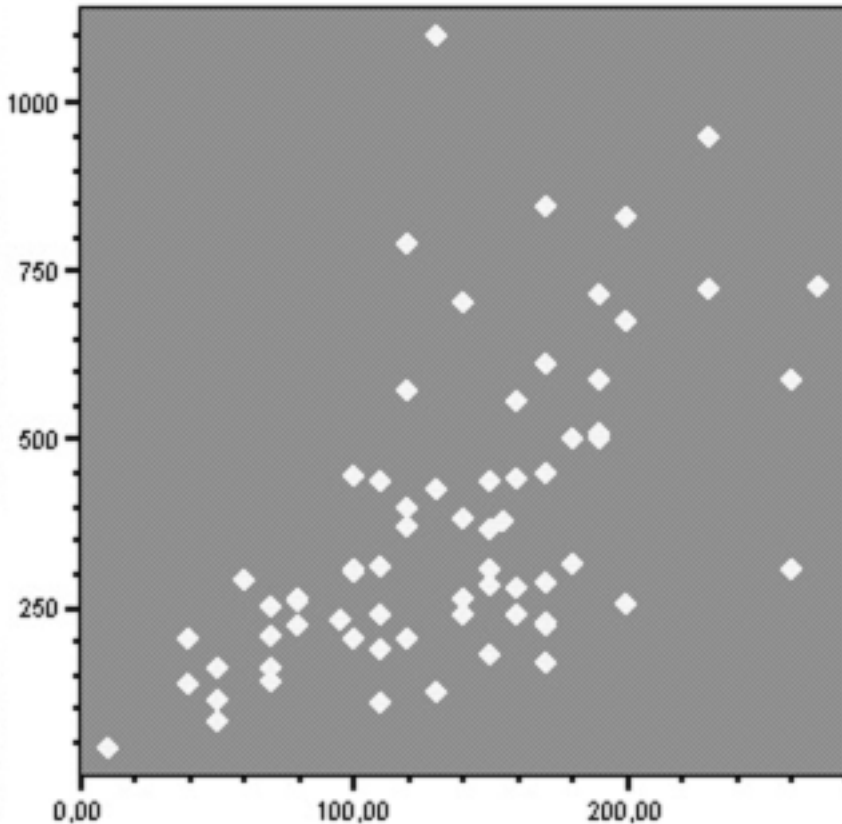


Discussion

Despite the fact that our study has confirmed that there is a clear correlation between the dose of methadone and its plasma level, and also that majority of patients who are stabilized on it had daily through-plasma concentrations between 200 and 400 ng/ml, we still had some interesting findings. Using clinical indicators to determine adequate methadone dose resulted in wide inter-individual dose variations.

Even if both distribution-of-frequency curves were bell-shaped, the dose distribution curve was less steep, with a peak further to the right than the curve for the distribution of frequencies of different plasma concentrations, which was steeper and had a peak further to the left. This finding suggests that a wider range of different daily doses is needed to achieve the optimum plasma concentrations. In other words, the doses required to achieve 250 ng/ml in plasma ranged between 60 and 270 mg of methadone per day (Graph 3). We have discovered that one third of our patients were stabilized at plasma concentrations, which were outside the lower or upper limit recommended by others (Graph 4).

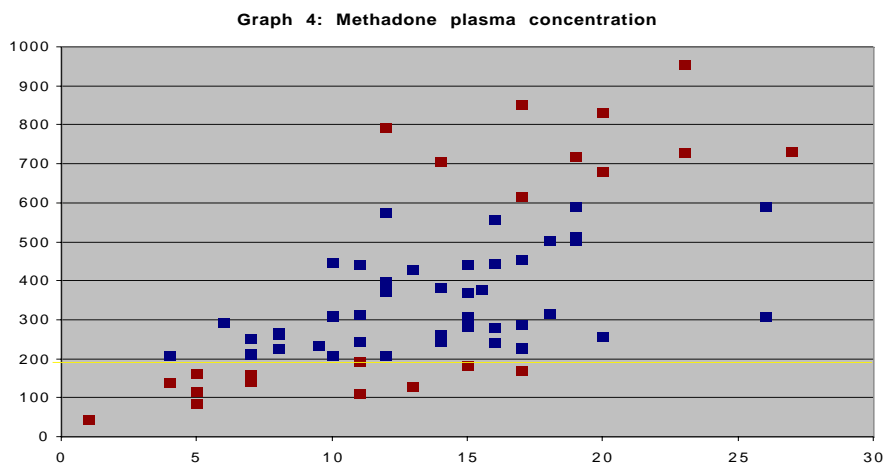
There were five concentrations above 700 ng/ml, and one over 1100 ng/ml among



stabilized patients. This is consistent with Maxwell and Shinderman [18], who reported that some patients with high doses had serum methadone levels of 800-1200 ng/mg when titrated to doses resulting in no signs of opioid overmedication; Leawitt et al. [13] even presented a case of 1800 ng/mg with no clinical signs of opioid overmedication and a severe opiate withdrawal syndrome at a concentration of 810 ng/mg with the same subject.

Similar situations have occurred on the other side of the spectrum at low concentrations. A similar proportion of patients with methadone concentrations below the lower recommended limit was found as for those with concentrations above the upper limit. We do not consider 17% as being insignificant. Again, no signs of withdrawal were observed and patients were stabilized. We found no reason to increase their dose.

One possible interpretation of our findings is that low methadone doses do not automatically result in low methadone concentrations in plasma. The same applies to unusually high daily doses of methadone, which do not necessarily produce high



concentrations in plasma. Bearing this in mind, we should not be restricted in our clinical practice to keeping to firm lower limit thresholds, or to any firm upper daily limit for methadone doses or even to a ceiling for plasma concentrations.

There are, in fact, patients who, to become stabilized, need unusually high or low methadone levels in plasma. The previous thinking could be turned the other way around, by saying that not only appropriate daily dose, but also appropriate plasma concentration show a high degree of inter-individual variation. The explanation for this wide spectrum lies partly in the variations in the degree of methadone metabolism specific to different patients, and partly in different interactions with other medications, or inter-individual differences in pharmacokinetics and pharmacodynamics.

Our findings suggest that neither daily methadone dose alone, nor methadone concentrations in plasma alone, can be interpreted as a univocal indicator of a patient's stabilization. It is, rather, the criteria derived from assessment of a patient's clinical condition that should set the ultimate guidelines for a doctor's decision as to whether daily doses of methadone in a methadone maintenance programme should be increased or decreased.

Plasma methadone concentrations should help provide clinical orientation in cases where the daily dose of methadone is relatively high, its level in plasma is low and clinical signs of withdrawal and/or craving are present. In case of this kind, the low level found in plasma supports an increase in the dose.

The limitations of the study lies in its naturalistic design and the limited size of the sample. In addition, rate of change is sometimes of greater clinical significance than absolute levels, so the peak through ratio could be measured.

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Treatment characteristics and retention in methadone maintenance: High and stable retention rates in a Swedish two-phase programme

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Summary

From 1967 to 1990, the Swedish methadone maintenance programme treated 345 heroin addicts, using a two-phase treatment model described in this paper. The retention rates remained remarkably stable throughout these 23 years, when measured as 1-year and as 3-year retention of newly admitted patients (mean 1-year retention was 86%, mean 3-year retention 73%) and 1-year retention of all patients in treatment (mean 89%). It is hypothesized that these high and stable retention rates might be associated with the high rates of social and vocational rehabilitation (between 71% and 81%) achieved during these years in the Swedish programme.

Key words: Methadone Maintenance - Retention rate - Predictors of outcome

Introduction

There are two broad treatment philosophies of methadone maintenance. One of these views opioid dependence as a manifestation of underlying social and psychological problems. Methadone can be used as a carrot, to entice patients into treatment, but the ultimate goal is abstinence from all drugs, including methadone. The other approach is primarily medically oriented and views opioid dependence as a chronic disease, with or without psychological components, but with drug craving as the main obstacle to rehabilitation efforts. The goal of treatment within this framework is, by blocking or reducing craving, to enable drug-dependent persons to achieve a new life-style. The resulting different treatment programmes are based on short-term or long-term maintenance philosophies [12].

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Caplehorn et al [2], using a somewhat different terminology, described a highly structured, paternalistic treatment, which is contrasted with an adaptive, libertarian system, each system with different effects on patient retention (Table 1).

Table 1. Programme characteristics, staff attitudes and retention in two different types of methadone maintenance, essentially according to Caplehorn et al. (1993)

	<i>Highly structured</i>	<i>Adaptive</i>
Staff attitudes	Paternalism, surveillance, control	Acceptance, support, encouragement
Ultimate treatment goal	Abstinence (including withdrawal of methadone)	Reduction or cessation of craving and drug abuse
Programme characteristics	<ul style="list-style-type: none"> • Reform and change oriented • We-they-feeling • Strict policy of involuntary discharge for programme violations • Mandatory counselling • Urinary drug monitoring 	<ul style="list-style-type: none"> • Adaptive • Empathy • Laissez-faire • Libertarian • No drug monitoring
Retention rate	Low	High

Common to all descriptions of the impact of treatment characteristics on retention in methadone maintenance is the assumption that only one treatment system is applied. In contrast, the National Swedish programme during its 23 years of existence from 1967 to 1990, applied a succession of the two treatment paradigms: a highly structured one followed by an adaptive. This combined, or two-phase treatment appeared to be compatible with a steady, high retention rate. After the Swedish methadone system had been split into 4 different programmes, a change which took place gradually, beginning in 1988, the prevalent programme in the capital, Stockholm, switched into a mono-phase, highly structured and confrontational system, with a rising rate of exclusion of patients and a rise in mortality rate above the nearly normalized mortality [6] existing before 1990. This development will be reported in a forthcoming study. Here we describe the stable, high retention achieved using our two-phase paradigm.

Methods

Treatment system: Heroin addicts referred to our clinic as candidates for methadone treatment were admitted to a 12-bed research ward, where their urine was regularly monitored 3 times weekly for drugs of dependence. There was initially a withdrawal phase lasting 1-2 weeks, where clonidine was administered to reduce heroin withdrawal distress. Before admission, patients had to fulfil the acceptance criteria of our programme: at least 20 years of age, a history of at least 4 years of compulsive heroin abuse as verified by earlier hospital records, at least 3 experiences of drug-free treatment programmes, patients should not be undergoing compulsory treatment, have been arrested or serving sentence [5]. Following heroin withdrawal, negotiations took place between the patient, hospital doctor and/or clinical social worker in order to decide a suitable vocation for

the patient after discharge. Failure to reach an agreement could prolong the drug-free phase. The patients soon learned what was expected of them and after a while newly admitted patients proclaimed on the very first day what would become their new vocation. For instance, they declared that they wanted to become a plumber, nurse's aid or an electrician. Induction of methadone took place as soon as these preliminaries were concluded. Patients were then taught how to behave and how to look to increase their chance of being accepted by an employer and, while still in hospital, they began to apply for work. Ideally, they were discharged after they had received a job, a place to live and with a daily methadone dose between 30 and 130 mg/day (mean 80 mg/day). The optimum dose was monitored, using mass spectrometric determinations of steady-state plasma levels of methadone [8]. Clinical social workers were generally involved in the finding of jobs and kept up contact with most of the employers. When problems arose, the hospital staff often got a patient's permission to discuss his or her difficulties with the employers and/or co-workers. In this way many jobs were saved and patients brought back to work after they had left in frustration. Work and studies were regularly monitored by university trained counsellors. A special group for outpatient treatment and follow-up was set up in 1972. To prove that they still had the job, patients sent in their monthly pay-check stubs. Their take-home privileges depended on that registration.

Retention measurements: Retention in treatment was measured in three different ways.

1. The 1-year and 3-year retention of newly admitted patients was recorded during the first 23 years of operation of this national programme.
2. In addition the yearly percentage of all patients who stayed throughout each year (irrespective of their time in treatment) was recorded.
3. Finally, the long-term retention was recorded for the first 10 years in treatment.

Long-term retention rates were calculated as the ratio (expressed as percentage):

$$\frac{\text{Number of subjects transferred to next year} \times 100}{\text{Subjects admitted before the beginning of a treatment year}}$$

Results

Altogether, 345 patients were admitted to our methadone maintenance programme during the first 23 years of its existence. Fig. 1 illustrates the yearly 1-year and 3-year retention rates for newly admitted patients. The mean 1-year retention during these years was 86% (range 60%-100%). The mean 3-year retention of newly admitted subjects was 73% (range 35%-100%).

Fig. 2 shows yearly retention rates, based on all subjects in treatment. The mean yearly retention rate was 88.8% (range 60-99%).

The lowest retention rate was recorded during the first treatment year, 1967, when only 5 patients were discharged to outpatient treatment and 3 (60%) stayed throughout the year. Table 2 shows both the yearly retention rates for each treatment year and the cumulative retention rates. A majority of the involuntary discharges occurred during the

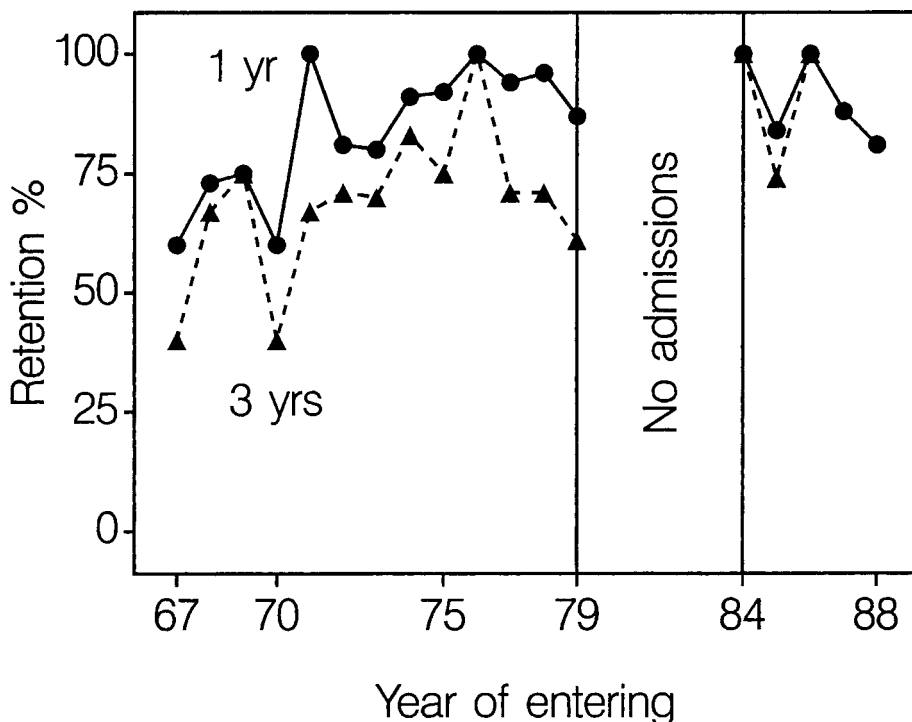


Figure 1. 1-year and 3-year retention rates among yearly cohorts of new admissions 1967-1990. For 5 years, 1979-1984, there was a temporary stop in new admissions, due to political tensions

first three treatment years (median 1.7 years). The voluntary discharges occurred later, after a median 5.0 years. The cumulative retention figures show that after 9 years 35% were still in treatment and after 10 years 29% (Table 2).

Most of the 46 voluntarily discharged patients managed to stay drug-free, continued working and had a continuously low mortality rate [6]. The most common reason for involuntary exclusion was repeated poly-substance abuse (Table 3). When patients had been admitted to an emergency ward for an overdose of hypnotics, they were warned that another such incident would result in exclusion, due to the increased risk of a fatal outcome from this drug combination. As a rule these overdoses occurred among patients who failed to follow several instructions in this programme. Patients who were imprisoned during treatment knew that they could reapply for treatment following their release. Patients excluded for programme violations were told when they could reapply for treatment. Those who were considered to be manageable had to stay outside for at least 6 months, while the rest could not reapply before 2 years had passed.

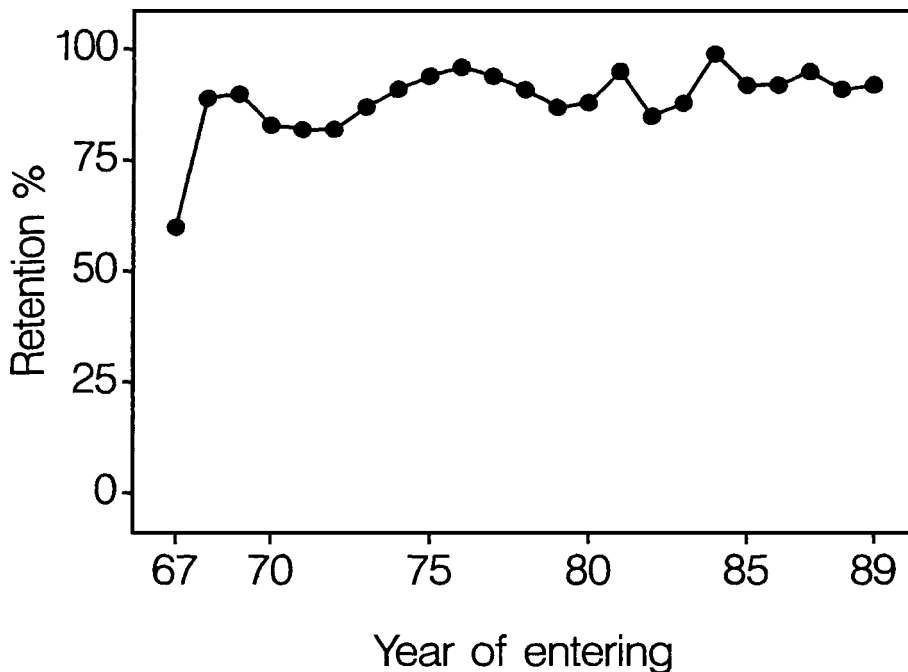


Figure 2. Percent patients remaining in treatment each year, from 1 January to 31 December during 1967-1990

Fig. 3 shows the percentage working or studying full-time the year before entering treatment and during the first 5 years of treatment. During the third to fifth year of treatment the percentage employed or studying varied between 71% and 81%. Forty-four patients (13%) had a job before entering treatment and 1% were studying.

Discussion

In the early American methadone maintenance programmes of the 1960s, high retention rates were, for instance, reported by Gearing [4], who found a yearly retention of 81% among the 2,325 patients admitted during the first four years. In their review of the first ten years' experience with methadone maintenance, Dole and Nyswander [3] expressed their concern about diminishing retention rates during the seventies. In the first five years, 1965-69, there had been a sensational 98% who continued to remain in treatment for at least one year; but between 1970 and 1973 the one-year retention rate dropped to 61%, and later to 59%.

Bayer and Koenigsberg [1] also reported a marked decline in 6-month retention during the period 1964-1976, when 78,498 first admissions were studied in New York

Table 2. Percentage long-term retention during the first 10 years of treatment

<i>Methadone treatment (n=345)</i>			<i>Voluntary discharge (n=46)</i>			<i>Involuntary discharge (n=96)</i>				
Treatment year	Transferred to next year	Adm. before this year	Died this year	Alive. Not in MT	Re-admitted	Dead	Alive. Not in MT	Re-admitted	Dead	Long-term retention %
1	278	323	2	3	0	1	24	2	14	86
2	207	254	0	4	1	0	5	0	7	81
3	155	211	2	3	0	0	9	2	2	73
4	118	194	6	6	1	1	2	1	3	61
5	100	174	2	2	0	1	0	0	0	57
6	88	174	0	2	2	1	4	1	2	51
7	79	174	2	2	0	1	1	0	3	45
8	63	169	2	3	4	0	2	0	0	37
9	59	169	1	1	1	0	0	0	1	35
10	49	169	2	2	1	0	4	0	1	29
11-23	0	---	2	2	1	0	4	1	1	--

Table 3. Reasons for discharge from methadone maintenance

Reasons for discharge	Male	Female	Total	Percent
1. Voluntary	36	10	46	13.3
2. Imprisonment	34	2	36	10.4
<i>Heroin smuggling</i>	2	1		
<i>Cannabis smuggling</i>	2	0		
<i>Drug trafficking</i>	8	1		
<i>Burglary</i>	16	0		
<i>Drunken driving</i>	2	0		
<i>Weapon theft</i>	2	0		
<i>Violence</i>	2	0		
3. Programme violations	42	18	60	17.4
<i>Repeated poly-substance abuse</i>	40	17		
<i>Repeated cheating with urine tests</i>	2	1		

City. During this period the retention rate of each successive admission cohort dropped markedly. Until 1970 an average 91% of all admissions remained in treatment for 6 months, but in 1975-76, the 6-month retention had dropped to 62%. When a couple of studies were carried out in the Nineties, comparing methadone and buprenorphine maintenance treatment, 6-month retention rates of 68% [10] and 52% [11] were reported in treatment groups receiving adequate methadone doses. Obviously, the yearly

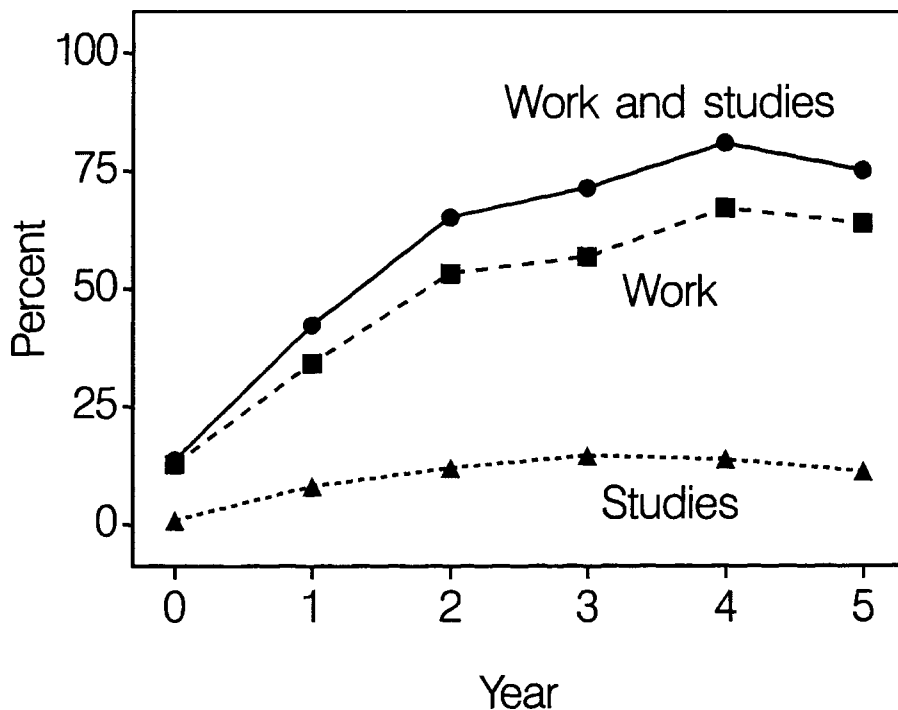


Figure 3. Percentage employed or studying during the first 5 years of treatment. Time point 0 shows the percentage employed (13%) and studying the year before entering treatment

retention rates must have been lower.

With this background, the stability of a high yearly retention within the Swedish methadone maintenance programme for 23 years is remarkable. This encouraging result may have to do with our unusually high rate of vocational rehabilitation. A selection of patients willing to abandon their drug habits and take up work may have turned to our treatment programme, and this high social and vocational rehabilitation rate also seems to have been stable over the years. Between 71 and 81 per cent of our patients acquired regular work, relief work or began studying full-time within 3-5 years of treatment initiation, with similar results for men and women [7]. The year before methadone induction, 13% were working and 1% studying; during the Eighties the yearly percentage of those employed or studying full-time varied between 59% and 81%.

The initial, temporary application of a highly structured and paternalistic program (but with no recommended time limit for methadone maintenance), obviously did not cause a great reduction of retention time, as predicted by Caplehorn et al. [2]. The strong focus on vocational rehabilitation in the Swedish two-phase treatment design seems to have enabled our successful patients to feel pride and hope, and accept responsibility.

In contrast, in our neighbouring Scandinavian country, Denmark, nearly all methadone maintenance patients (around 5,000) were granted an early retirement pension, sufficient to support the individual without working for an income [9]. After some years the Danish methadone maintenance patients were found to have taken up new kinds of abuse, including alcohol, amphetamine, cocaine and hypnotics. Later still there was an outbreak of suicides among the Danish patients. Obviously, a permissive attitude had not promoted an efficient rehabilitation, and although perceived as benevolent it may in fact have been more patronising than a treatment ideology requiring patients to take responsibility for supporting themselves. In Sweden, drug abuse remained low among our patients [7], and there was no endemic outbreak of suicides.

Thus, a succession of an initially highly structured and controlled treatment paradigm, followed by an adaptive model supporting a gradual increase in patient autonomy, appears to have been a successful design for many years. The political decision to discontinue the Swedish National Programme appears to have been unfortunate.

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