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Methadone maintenance treatment: an update

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Abstract Available data (this review includes old major articles and recent articles) show that, although results are heterogeneous, methadone maintenance treatments (MMTs) have a real efficiency not only to reduce illicit opiate abuse (50–80% of patients under MMT did not use heroin in the preceding month) but also to reduce criminality, HIV risks and mortality, and to improve social rehabilitation, without inducing other alternative substance abuse. A minority of patients (perhaps 5–20%) stay on MMT on a very long-term basis (more than 10 years). Efficiency of MMTs are rather poorly related to patients' variables, with the exception of a moderately deleterious effect of a low age at onset of opiate dependence, a precocious or high involvement in criminality and an abuse of non-opiate drugs. On the other hand, variables related to treatment play a more important role in explaining heterogeneity of results. Optimal daily dose, high quality of medical and psycho-social services, clear orientation towards social rehabilitation and treatment retention (to allow a sufficient duration of treatment) and slow detoxification regimen of well-stabilized patients are all factors contributing to better results.

Key words Methadone · Opiate addiction

Introduction

Methadone maintenance treatment (MMT) was developed in the 1960s [27] and has been the topic of many controversies throughout its history [44]. Human immunodeficiency virus (HIV) infection has contributed to give it a new relevance. Many studies on MMT have been published. In this paper, combining results of relevant old papers and recent studies, we propose an update on the topic of the efficiency of MMT. In the first part, we present data

using different measures of efficiency: heroin use, criminality, social stabilization, non-opiate drug abuse, mortality, HIV, retention rate, methadone stopping. In the second part, we discuss the factors which can influence the efficiency of MMT: patient-related factors, and factors linked to treatment methods and methadone maintenance programme (MMP) characteristics. As we will discuss, many factors may influence MMT results. Consequently, a part of the heterogeneity of the MMT efficiency may be attributed to differences concerning various factors: inclusion and exclusion criteria, psychosocial treatment and treatment policy. A particularly sensitive methodological issue concerns the way patients drug use is measured: urinalysis and/or self-report are the usual methods. However, their reliability is not very different [107]. It perhaps depends on some of their specific characteristics such as frequency of urinalysis or confidentiality of self-reports.

Efficiency of MMT**Heroin use**

The rate of patients under MMT with no heroin use in the preceding month is roughly between 50 and 80% as shown in Table 1.

Some studies allow the comparison with placebo. Newman and Whitehill [65] treated 100 opiate-dependant patients in Hong Kong with 60 mg of methadone for 2 weeks. Then, on a double-blind basis and during an 8-week period, patients were allocated to placebo or methadone maintenance (mean dose: 97 mg per day). As soon as a patient had six consecutive positive heroin tests, or failed to attend the clinic for six consecutive weeks, he was withdrawn from the study. At week 32, there remained 76% of the patients in the treatment group and 10% in the placebo group. Strain et al. [94] gave their patients ($n = 247$) 25 mg of methadone the first week, and dose changes were implemented from weeks 2–5; patients were then stabilized on 50, 20 or 0 mg of methadone by week 6 of the treatment. By week 20, only the 50 mg

Table 1 Efficiency of methadone maintenance programmes (MMPs) to reduce heroin use: non-comparative studies

Author, year published and reference	Characteristics of study group (<i>n</i> = number of patients)	Results
Bale et al. 1980 [1]	<i>n</i> = 59 - 1MMP	53% of patients with no heroin use in the preceding month
McGlothlin and Anglin 1981 [57]	<i>n</i> = 238 - 3MMPs	34 to 54% of the whole time in treatment with no narcotic use
Ball and Ross 1991 [2]	<i>n</i> = 339 - 6MMPs	83% of patients with no heroin use in the preceding month
Condelli and Duntzman 1993 [18]	<i>n</i> = 526 - 17MMPs	83% of the year following admission with less than weekly heroin use
Kang and DeLeon 1993 [46]	<i>n</i> = 152 - 1MMP	49% of patients with no heroin in the preceding month

treatment group had a significant reduced rate of opioid positive urine samples (56.4% versus 67.6% and 73.6% for the 20 mg and 0 mg groups, respectively). The difference is even higher if we only consider the patients still in treatment at week 20 [95].

Other studies compared MMT and other treatment modalities. In the above-mentioned study by Bale et al. [1], the 1-month abstinence rate 1 year after admission of 53.4% in the MMT is comparable to the rates of two subgroups among the patients in a therapeutic community: 33.3% for those who had been in a therapeutic community for less than 7 weeks and 62.7% for the others. The results need to be interpreted by taking into account the fact that MMT retained 29% of those assigned, against 18% for the therapeutic communities. Data of the DARP (Drug Abuse Reporting Programme) [89] show that, in the year after treatment admission, MMT reduced opiate use in a similar way to therapeutic communities and drug-free treatment. A report of Vaillant [100] on a population of 100 heroin addicts states that 15 MMT exposures were followed by 1 year of abstinence in 67% of the cases against 3% for 361 hospital detoxifications or 363 short imprisonments, but 71% for 34 imprisonments followed by at least 1 year parole.

As a whole, such data show that MMT strongly reduces heroin use. For a majority of patients, there is no heroin use in the preceding month and, among the remaining ones, only a minority continue daily use.

Criminality

Considering all the patients, being under MMT is associated with a clear criminality involvement decrease. Ball and Ross [2] observed among 617 patients a 79% reduction of the annual number of offenses between the year before admission and the more recent year in MMT. This reduction concerns the number of subjects involved in crime and, for those involved, the number of offenses per year. Reno and Aiken [75] described subsequent lower criminality scores among people who remain on methadone treatment as compared with those who left within 2 months after admission.

After 1 year of MMT, 89% of the 51 patients of Lehmann et al. [52] had no links with the judicial system

versus 58% at entry. In the three programmes examined by McGlothlin and Anglin [57], the mean number of crime-days per non-incarcerated year fell from the range 96–131 to the range 24–70 between the period of addiction before admission and the period under treatment. In the same study, the mean time incarcerated decreased from the range 28–39% to the range 13–22%. In another study, the same authors [56] observed a decrease of the mean time incarcerated from 14% to 3% and an increase to 18% when an MMP was closed. Maddux and Desmond [60] found that after 10 years, patients who cumulated at least 1 year of MMT had spent half the time in prison than patients who did not (23 months against 46 months; *n* = 95 and 77).

Comparative studies add further evidence. In the work of Newman and Whitehall [65], addicts under placebo have double the number of convictions during their enrolment in the study than the patients under MMT. Bale et al. [1] obtained a rate of incarcerations after 1 year at 10.2% for subjects under MMT against 21.3% for the subjects who spent less than 7 weeks in therapeutic communities and 4% for the others (therapeutic community groups as a whole: 12.7% rate). In the large DARP study, MMPs do better than therapeutic communities and drug-free programmes for the variable "any jail", 1 year after intake [89]. In Denmark, a policy of limitation of access to MMTs was followed by a rise in criminality and only a very small group of patients under almost constant methadone treatment for 2 years had a decreasing number of criminal convictions [80].

Social rehabilitation

McGlothlin and Anglin [57] reported that in three MMPs the mean time in full-or part-time employment ranged from 38% to 47% during the addiction career and from 52% to 62% during the treatment period. In another programme [56], they observed a rate increase from 32% to 44% between the two periods and stabilizing at 43% after closure of the programme.

Patients who cumulated more than 1 year of MMT over 10 years had a higher number of months at work than the patients who did not: 49 months against 35 months [60]. In Canada, 1 year after admission to an MMP, Lehman

Table 2 Retention rates in methadone maintenance programmes (MMPs)

Study	Numbers of cases and MMPs studied	6-month retention rate	1-year retention rate
Bale et al. 1980 [1]	<i>n</i> = 59	–	29
Ball and Ross 1991 [2]	<i>n</i> = 126 6 MMP	–	38 (range 25–44)
Caplehorn et al. 1993 ^a [15]	<i>n</i> = 238 2 MMP	81 (range 79–82)	61 (range 58–71)
Fisher and Anglin 1987 ^a [30]	<i>n</i> = 347 3 MMP	82 (range 75–93)	70 (range 56–85)
Lehman et al. 1993 [52]	<i>n</i> = 51	–	73

^a calculated by us from data survival of curves

et al. [52] described an increase of job or school involvement from 60% to 86%. In Denmark [80, 81], no favorable relationship between MMT and employment is found, whereas in Sweden [38], a strong favorable relationship is observed: 12 out of 17 were gainfully employed 2 years after random assignments to an MMT against 1 of 17 in the untreated group.

In the comparative study of Bale et al. [1], 1 year after admission to treatment, 51% of subjects under MMT were working or attending school versus 51 from those in therapeutic communities (65% if they stayed at least 7 weeks in treatment, 36% if they left before). Focusing on daily life (domestic and leisure activities) and quality of life rather than on a "hard" outcome criterion such as employment, Reno and Aiken [75] observed a clear improvement 2 months after MMP admission. Therefore, MMTs have a moderate but effective positive influence on employment of addict patients.

Non-opiate drugs abuse

Of the patients in MMP 15–40% have an alcohol abuse problem [2, 28, 57, 76]. These rates of alcohol problems are 1.5–3 times higher compared with the period of addiction preceding the programme intake [57, 76, 87]. When patients are readmitted several times to MMPs, alcohol consumption increases and decreases as patients are on- or off-methadone [72]. This could suggest that methadone promotes alcoholism or that one addiction substitutes another. This conclusion has to be criticized in the light of several remarks. Firstly, DARP data [89] show that all treatment modalities, including therapeutic communities, (with the exception of drug-free programmes), are followed by an increase in alcohol use 1 year after treatment admission. Secondly, as patients remain in MMT for several years, alcohol abuse tends to decrease [2], and after methadone detoxification, after a transient increase during the detoxification process, alcohol consumption decreases to the pretreatment level [76]. Thirdly, data analyzed from the nationwide Treatment Outcome Prospective Study (TOPS) in the USA, comparing heavy alcohol use before and 1 year after MMT admission, showed that this variable was relatively constant across the two time periods,

and with no significant relationship to continuous enrolment in MMP or weekly use of heroin [29].

The relationship between cocaine and MMT is complicated by a period effect. Cocaine use has seen a clear increase during the 1980s and the reports of such an increase among patients in MMT during the same period [2, 22] is not a surprise. Nowadays, in the USA, 20–75% of methadone-maintained patients have used cocaine in the preceding month [2, 22, 28, 94, 106]. It is not known if such a situation is current in any other countries. In Switzerland, cocaine use among methadone-maintained patients is lower (personal data). Patients on MMT generally engage in relatively low-dose cocaine use especially when compared to non-opioid-dependant patients applying to cocaine treatment programmes [48]. There is no long-term data available and cocaine use development is still too recent to allow for any comments on long-term prognosis of cocaine use among methadone-maintained patients. Some authors are looking for a decreased cocaine use on opioid maintenance with the mixed agonist-antagonist buprenorphine as compared with the pure agonist methadone. However, current results do not support this hypothesis [70] and in the methadone placebo controlled study of Strain et al. [94], the rate of urine samples found positive for cocaine increases as the daily methadone dose decreases, becoming maximal for that of the placebo group.

Sedatives, the most used being the benzodiazepines [2], are frequently abused among patients in MMPs: from 18% in the preceding month in the Ball and Ross study [2], to a 44–46% range in the six preceding months in the Iguchi et al. work [43]. However, there are no data to suggest that sedative abuse persists or even increases as patients remain on MMT. On the contrary, the proportion of patients having used benzodiazepines and other non-barbiturate sedatives decreases with the time spent in an MMP [2, 29]. Cannabis use is also decreasing with time spent in MMPs [2] and cannabis is the only drug with a significant annual decrease for the patients interviewed both in 1985 and 1986 in the Ball and Ross study [2].

In conclusion, alcohol, sedatives, cocaine, cannabis use or abuse are frequent among subjects in MMTs. Long-term data (which are as yet unavailable for cocaine) do not suggest that MMTs make the problem more serious. On the contrary, things are improving with time spent in

MMPs [2, 29], people using heroin less than once a week are less likely to use other substances than patients continuing to use heroin at least weekly [29]. Finally, it has to be stressed that preadmission use of a substance clearly predicts its use after MMP admission [29].

Mortality

To evaluate effects of MMT on the mortality rate of addicted patients raises some methodological difficulties: mortality rate may be very different according to the way deaths are recorded (problem of the numerator) and addiction cases are identified (problem of the denominator) [33].

A few studies offer comparative possibilities. In the placebo study of Newman and Whitehill [65], where most of the patients were quickly excluded from the study and switched to open MMT, there is no significant difference between the two groups for the number of deaths occurring during the 3 years of observation (respectively 1 and 3 in the control group, $n = 50$, and in the treatment group, $n = 50$). In a 2-year Swedish randomized study, there was no death in the MMT group ($n = 17$) and two deaths in the no-treatment group ($n = 17$) [38]. After these 2 years, patients of the no-treatment group were allowed to enter an MMP: 8 did so. After a few more years, of the 25 patients admitted to the MMP, no one had died against four out of nine among the others. Long-term results of the same team clearly confirm this trend: the mortality rate is eight times higher among untreated controls as compared with patients under MMT [37]. An Australian study recently suggested that MMT patients were one-third as likely to die as those who had left treatment.

Cushman [21] examined the rate of deaths among 225 patients discharged from treatment. Those detoxified with the approval of the staff ($n = 89$; mean time since discharge: 2.4 years) had a mortality rate significantly lower than those who were discharged for infractions of the clinic's rules ($n = 66$; mean time since discharge: 2.8 years): 2.9% vs 5.0%. Maddux and Desmond [60], after 10 years, observed that 16.8% of the subjects with more than one cumulated year of MMT had died against 10.4% of those with less than 1 year (difference not statistically significant). Weber et al. [102], in a study focusing on HIV evolution, measured an annual rate of deaths (calculated by us) of 5.4% among 80 HIV positive patients on MMT against 21% among 124 HIV positive persistent injecting drug misusers (mean follow-up: 16 months). Segest et al. [81], in a context of unwelcome MMT, found a rather high mortality rate of 3.3% among a sample of 169 opiate addicts followed for 8 years and that the mortality rate decreases as a function of both the duration of MMT and the grade of social stability. In one extreme, the socially unstable patients with a very short time in MMT had the highest annual death rate (7.6%; 2.2 if socially stable). In the other extreme, the socially stable patients with considerable methadone treatment had the lowest annual rate (0.5%; 3.3 if socially unstable). This long-term data confirms other data established on a shorter term by

the same research group [80], showing that, in the context of aiming to reduce MMP, only those drug addicts who had been under almost constant MMT had a low lethality rate. Recently, Bell et al. [5] added further evidence to the hypothesis that patients who apply for MMT but are rejected, or do not complete the assessment procedure for admission, have a higher mortality rate than those admitted: 2.8% of the annual rate for 58 patients rejected and 26 with admission assessment not completed, against 0.6% for 291 patients admitted to the MMP. Although not homogeneous, results are clearly in favor of the positive effect of MMT on the mortality rate.

HIV risk reduction

MMT access is only one of many factors (such as access to syringes, access to counselling about risk behavior, quality of treatment programmes and retention rates, characteristics of local addict subculture) able to modify HIV risk at a given location [98]. This could explain why no relationship between HIV rate and methadone access has been found in six countries [35]. HIV risks depend on time effects (cumulative number of years at risk) and on cohort effects (when the years at risk occurred). Indeed, the AIDS epidemic has contributed to modify addicts behavior. A decline in the rate of current intravenous drug use among treatment-seeking opiate users [79] or HIV seropositivity at admission to MMT [86] has been observed. Having been admitted to an MMP before HIV infection being widespread and being socially rehabilitated with long-term maintenance on methadone could have protected drug abusers from HIV infection, as suggest zero-rates of seropositivity observed among well-stabilized patients on MMT before the spreading of HIV in New York [66] or Chicago [3].

By reducing heroin use, MMT reduces HIV infection transmission risks. Conversely, intravenous use of other drugs, such as cocaine, may increase this risk. However, several studies exhibit reassuring results concerning intravenous use and needle-sharing. Ball and Ross [2] found in 324 patients that 36% had shared needles during their last period of intravenous drug use and that currently, in the month before the interview, only 9% of the initial sample continued to practice intravenous use and needle-sharing and, what is more, did so at a lower frequency. Longshore et al. [54] compared 105 patients enrolled in MMT at the time of the interview with 153 patients who were not currently in MMT (although 69% reported some treatment in the preceding year). The rate of patients who shared needles or syringes in the preceding year was lower in the first group (63% vs 79%, $P < 0.05$), and among sharers, the frequency of sharing was also lower than in the second group. This relationship between MMT and needle-sharing reduction persisted after injection frequency and drug-users background characteristics were controlled. It is of interest to note that the author's efforts to identify treatment processes liable to explain this relationship were not successful.

Being in MMT is associated with a reduction in the number of partners and exchange of sex for money or drugs, but not with a higher condom use [101]. Condom use is not systematic among HIV seropositive methadone-maintained patients [10, 85]. Once contaminated, addicted patients could have a slower progression of the disease if they follow an MMT than if they persist in their drug misuse, as is strongly suggested by a Swiss study [102]. This has to be related with studies showing that significant abnormalities of cellular immunity in parenteral heroin abusers can be normalized by successful long-term MMT [67].

In conclusion, available data invite us to consider that MMT contributes effectively in preventing HIV infections spreading among opiate addicts, even if it is only one factor among many.

Retention rate

Keeping patients in treatment is an important condition to obtain other therapeutic results. The retention rate is now considered an important indicator of efficacy for an MMP.

Table 2 shows that retention rates 1 year after treatment admission range from 25 to 80%.

The ability of methadone to retain patients in treatment is, at best, demonstrated in the two placebo-controlled studies mentioned before: in the Newman and Whitehill study [65], the retention rate after 32 weeks was 76% in the methadone group versus 10% in the placebo group (patients being excluded after six consecutive positive heroin tests); in the Strain et al. study [94], the retention rate after 20 weeks was 52% in the methadone (50 mg daily) group and 21% in the placebo group. MMT shows better results than therapeutic communities for retaining patients [1]: 29% of retention at 1 year against 18% having spent at least 7 weeks in a therapeutic community.

MMT stopping methadone use and long-term prognosis

Stopping methadone is successful only if therapeutic results, such as no longer using opiates, are preserved. This may be described as a survival curve related to the time elapsed since methadone detoxification. Such results will be presented in function of this variable.

Firstly, when patients are selected for progressive methadone interruption, not all manage to achieve a zero-dose of methadone without drug use or asking to stop interruption: only 25–75% manage to do so [21, 64, 83, 90].

With 6 months of drug abstinence after completion of MMT in a private physicians network as a criterion of success, Meystre-Agostoni et al. [63] observed that 17% of the treatments were successful (no data were given about the context of the decision of ending the treatment). For selected patients of the first American MMP, Cushman and Dole [23] stated that after a mean of 9 months (range 2–29 months) since methadone interruption, 71% of their 48 patients remained apparently drug-free and

functioned well. Ball and Ross [2] reported that one-third of the patients (234 of 633) left the treatment during the 1-year follow-up. Of them, 105 were reinterviewed. With a mean of 7.2 months since their leaving MMP, 68% had resumed intravenous drug use. There was no difference between the 23 who had been detoxified after having completed treatment in the programmes and the others (70% vs 67%).

Three to 24 months after detoxification, Pugliese et al. [73] found that 80% of the patients who had been detoxified with MMP staff approval ($n = 15$) were still drug-free against 10% of the others ($n = 17$). In the Cushman study [21], after a mean of 2.9 years, these rates were respectively 46 ($n = 89$) and 7% ($n = 108$).

In Basel [51], 6–48 months after detoxification 30% of the patients having finished their treatment ($n = 20$) had poor outcomes against 51% of the patients having interrupted their treatment ($n = 27$).

In a group of 38 patients selected for their good prognosis, Riordan et al. [76] obtained, 6–44 months after stopping methadone, a narcotic abstinence rate of 79%. In the Dole and Joseph study [26], 34% of 167 patients detoxified with staff approval were still opiate-free after 2 years, without any others problems (25% of the initial sample could be added, who were narcotic free but with other addiction-related behavioral problems); among the 573 patients detoxified for other reasons, there were only 2% still opiate free after 2 years.

Relapse probabilities decrease with time: more than 80% of the relapses occur in the first year [2, 21].

As already reported in the above-mentioned studies, MMT interruption is not always the result of a well-prepared therapeutic decision. Uchtenhagen [99] estimates that the ratio of drop-out rates to the rates of regular graduates (who are withdrawn from methadone and discharged with staff approval) is more than one: literature data confirm this assertion with ratios ranging from 1 to 5 [2, 21, 26, 73].

Long-term follow-ups are rather scarce. Stimmel et al. [92] reported that 6 years after detoxification, 83% of 58 persons of those who completed treatment and detoxified with staff approval were narcotic free compared to an average of 16% narcotic free of those detoxified for other reasons ($n = 277$). DARP data [87] showed that after 6 years of a sample of 384 patients from different MMPs, 20% reached immediate opioid abstinence (19% without further treatment and 1% with continuous treatment) and 42% reached delayed opioid abstinence (28% without further treatment and/or jail/prison once abstinence had been reached, 14% with continuous treatment). Those remaining included 20% of the patients with heavy and sustained opioid use. On such a long-term basis, MMT treatment gives similar results to therapeutic community and drug-free treatments [87]. Results of a 12-year follow-up [88] confirm the 6-year results. In the Maddux and Desmond study [60], when examining the 10-year outcomes, 95 chronic opioid users, who had spent at least one cumulative year in MMT, differed from 77 chronic opioid users, who had spent less than one cumulative year on MMT, by

Table 3 Influence of socio-demographic variables before admission on methadone maintenance treatment results

Variables	Studies demonstrating a negative influence	Studies failing to demonstrate any influence	Studies demonstrating a positive influence
Sex (being male)		[18], [21], [26], [34], [41], [45], [46], [52], [56], [69], [72], [83], [92]	
Marital status (being single)	[41]	[20], [34], [52], [69]	
Social origin (low level)		[69], [72]	
Educational level (low level)		[18], [26], [34], [52], [92]	
Age (being young)	[9], [17], [21], [41], [72], [89]	[2], [21], [45], [46], [52], [56], [67], [76], [78], [92]	
Ethnic factors (being a black or spanish american)	[42], [45], [78], [73]	[2], [18], [26], [34], [72], [83], [92]	[46], [76]

exhibiting a lower voluntary abstinence rate (20% vs 40%), a higher rate of MMT continuation (27% vs 0%) and a lower rate of incarceration (13% vs 27%).

An important problem is that most patients need several treatments before obtaining results, and successive treatments are often of different types. In the DARP study [87], two-thirds of the patients who became abstinent did so after a relapse and a new treatment and/or a prison sentence. In the Ball and Ross study [2], the mean number of prior treatments is 3.8. Such a phenomenon raises methodological difficulties in evaluating the long-term effect of a given intervention.

Some patients receive MMT on a long-term basis and clinical case studies lend some rationale to this approach [68, 104]. It is difficult to evaluate how many there are. In the Ball and Ross study [2], 5% of subjects had a duration of stay in the MMP of 10 years or more: every year, only a few percent of the patients (4–6%) leave the programme and are still abstinent 1 year later. In the DARP study [87], 5% of the successful patients are still in treatment after 6 years and in the Maddux and Desmond study [60], 27% of the clients who spent more than one cumulated year in MMT, are still in treatment after 10 years.

In conclusion, we can say that results are not very homogeneous and allow only very cautious estimations:

- 25–75% of the patients who try to reach a zero-dose of methadone manage to do so.
- after methadone interruption, the relapse rate after 6–12 months is 10–70%, and is higher among people having left MMT without staff approval.
- a minority will receive methadone on a long-term basis (more than 10 years): they could represent 5–20% of the patients admitted into MMPs.

Variables related to efficiency

Sociodemographic variables before admission

Table 3 shows the lack of influence of the sociodemographic variables (a slight negative effect of young age may be an exception).

Clinical variables

Data about the relationship between family disturbances and MMT outcomes are rare and contradictory: Lehmann et al. [52] reports less drop-outs and more abstinence after 1 year among patients with foster care, (but not for those with antecedents of parental abuse). Olie et al. [69] obtain opposite results for foster care, and Powers and Anglin [72] found no relationship between the number of required MMT sessions and variables such as being raised by both parents, the quality of family relations of the patients or parental alcoholism.

Age at onset of opiate dependance influences MMT results, whereby later onset leads to better results [2, 26, 46, 72, 76], even if it is not systematic [69]. In the Kang and De Leon study [46], the age of onset of addiction is correlated with age of onset of criminality, and only this last variable remains negatively correlated with abstinence of intravenous drugs after stepwise discriminant analysis. Length of addiction career is sometimes not at all [2, 65, 83], positively [9], or sometimes negatively [26, 46, 72, 76] correlated to outcomes.

Criminality involvement in the pretreatment period also seems to be a moderate predictor of a less favorable evolution [2, 45, 46, 56, 57, 75, 89], although not always [40, 52, 69, 72].

Psychiatric comorbidity effects on MMT outcomes is another problem. Two important studies in the 1980s stressed that associated psychiatric symptoms, as evaluated by the Addiction Severity Index, are correlated with bad outcomes [59] and that depression and life crises increased the treatment readmission rate [49]. However, in both studies, methadone-maintained patients represented a minority in the studied sample. In the McLellan study [59], the relationship between psychiatric symptoms and poor outcomes was weaker for MMT than for other opiate addiction treatment modalities. A few studies concern specifically MMT. They use symptom lists or scales and no diagnostic instrument. For a study using the HSCL90 symptoms checklist and showing, after stepwise discriminant analysis, a significant correlation between depression and persistent intravenous drug use during MMT [46], we found two studies reporting no relationship between 1-year evolution and psychiatric symptoms. One [2] used the Psychiatric Severity Scale of the Addiction Severity

Index, and the other [52] used an evaluation of emotional well-being included in the Heimler Scale of Social Functioning.

An Australian study [16] suggests that psychologically disturbed patients (as rated with the General Health Questionnaire scores) are more likely to be expelled from or otherwise leave treatment than those who are less psychologically disturbed and who continue to use heroin.

Antisocial personality and social instability have been correlated with poorer results [78, 81].

Neither the failure of other therapeutics [69] nor prior MMT sessions [2, 52, 63, 72, 75] seem to influence the outcome after admission to an MMP. Abuse of non-opiate drugs before or at admission (including the first 2 months of treatment) seems to be correlated with rather poor outcomes concerning opiate abstinence, criminality, treatment continuity or high-risk behaviors [8, 18, 45, 75, 78, 106], even if an exception concerning alcohol must be mentioned [28].

HIV infection has rarely been considered. According to available data [10, 69], HIV seropositivity does not preclude abstinence and stability during MMT.

Variables related to the treatment

Characteristics

Evaluating the impact of a multiprofessional committee established to regulate and limit MMT, a Danish study [80] reported that only those addicts who had been under almost constant methadone treatment had a low mortality and a decreasing number of criminal convictions. Their results suggest that there is no rationale in making access to methadone treatment more difficult. An Australian study [5] similarly demonstrated that too strong and cautious regulations concerning access to MMP only served to prolong the applicants illicit drug use and delay their entry to treatment. A Swiss study carried out in Zurich [97] reports a steep increase in cases following the new regulation of MMTs, making access to the latter easier. This suggests that the prior restrictive regulation lead to the need for treatment not being adequately satisfied.

Making access to MMP easier could increase initial [91] and short-term [18] retention rates. In the case of a lack of room in standard MMPs, the access to an interim MMP with minimal prestation would improve short-term heroin use and long-term retention rates [106].

Allowing patients to receive sufficient daily doses of methadone is an important point. For one study with a small population sample showing no influence [6] or one study using administrators' answers suggesting that flexibility of individual doses rather than the amount of the daily dose per se is important for retention rates [11], there are a lot of large studies clearly demonstrating that higher dosages result in better outcomes whichever indicator we consider [2, 12, 13, 24, 36, 53, 57, 95]. In a recent review of the topic, it was concluded [7] that most of the patients require at least 60 mg of methadone racemate

per day and that, if needed, an increase of the dose to 80 or 100 mg, or even more, will improve outcomes. The influence of the daily dose consequently raises the question of the interest in monitoring the plasma levels to look for a therapeutic window. Although recent studies confirm that plasma levels above 100 or 150 ng ml⁻¹ are associated with better outcomes [4, 6, 53, 105], there are no clear data supporting a specific interest of monitoring to determine the daily dose in standard conditions. The main explanation is probably the relatively linear relationship between plasma concentration and methadone dose for most patients [105]; the question of a minority of patients with low [71] or very low [96] methadone plasma levels at usual daily dose remains unanswered.

Medical, psychological and social services vary greatly depending on country, public or private sectors or programmes [2, 84, 99]. When social services received during the first month after admission are evaluated by the patients as being of high quality, the 1-year retention rate is increased by a factor of 3.5 [17]. The Ball and Ross study [2] deeply scrutinized the influence of the MMP characteristics and services on outcomes, using the metaphor of "opening the black box". Their results strongly suggest that patients in MMPs with rehabilitation and long-term maintenance orientation, which also delivered more counselling and medical services to patients, and with more effective directors tended to have better outcomes than patients in MMPs where there was emphasis on administrative functioning rather than provision of services (even if these last MMPs were characterized by favorable staff/patient ratios in better facilities).

The highly positive effect of psychosocial services has been clearly confirmed by McLellan et al. [58], using a random assignment to one of three treatment groups for a 6-month clinical trial: if patients in group 1 (methadone alone, at least 60 mg/day, with no other services) reduce their opiate use, they show less improvement than patients in group 2 (same dose of methadone plus counselling) and patients in group 3 (same dose of methadone plus counselling, and on-site medical-psychiatric, employment, and family therapy) yet do better than patients in group 2.

One prospective study [90] found that offering a network support programme for detoxification time results in a non-significantly higher proportion of patients reaching the zero dose.

MMP rules and politics are not neutral. While allowing for patient variables and maximum doses of methadone, subjects assigned to a severe abstinence-oriented programme are more likely to drop out of MMT than subjects assigned to a more "laissez-faire" programme [15]. Discharge for persistent drug abuse leads to a very low retention rate [31]. Thus, applying a negative contingency contract (drug use induces a methadone dose decrease) results more often [78, 93], if not always [55], in a decrease in retention rate. Information of patients about their methadone daily dose is correlated with a better retention rate [17]. Allowing take-home methadone doses does not result in more positive urine tests [40]. Take-home methadone doses may be considered as an indicator and a recog-

nition of patients compliance and progress: in the Ball and Ross study [2], it is negatively correlated with opiate or cocaine use 1 year later.

Duration of treatment is positively correlated with drug abstinence during MMT [32, 78]. Sometimes, it is even the more strongly correlated variable [34, 46]. In the Ball and Ross study [2], the variable length of stay is prospectively significantly correlated with only one of five outcome indicators (last intravenous drug use), but the prospective approach applies a population with a relatively high mean length of stay (45 months). As argued by the authors, long-term patients may pass a threshold beyond which the length of stay has relatively few differential effects. At the beginning of the study, when they looked at the correlation between mean time in treatment on the one hand and intravenous drug use or reduction in crime on the other, they observed a clearly positive relation (even after 3 years of drug use). Hser et al. [41] report that an average time of 40 months in treatment is needed for their population to become abstinent. One study [61] found better results after ten years for patients having spent less than one year in MMT than for the ones having spent more than this. However, this concerns long-term results and others studies show a moderately positive effect of length of stay in MMT on the ability to remain drug free after methadone detoxification [2, 20, 26, 56, 73, 76, 92]. When looking at patients having detoxified with staff approval and being drug-free, their mean length of stay in MMT are from 30 to 52 months [2, 20, 26, 76, 92]. In fact, it is probable that the relation between the length of stay in MMT and the ability to remain drug free is an indirect one, with a chain of successive correlations between length of treatment – length of heroin abstinence in treatment – approval of detoxification project by MMPs staff – ability to remain drug free after detoxification. In favour of this hypothesis are data showing relations between length of heroin abstinence [2] or staff approval [20, 26, 73, 92] and ability to remain drug free. Moreover, the strength of the relationship between treatment duration and ability to remain drug free may be attenuated by a minority of patients doing well on MMT and who detoxify deliberately early in the course to attempt abstinence [45].

Detoxification regimen, defined as the time-related methadone dose decrease, influences the ability of patients to remain drug free. Methadone maintenance dose level prior to detoxification did not predict a difficulty in obtaining and maintaining abstinence [47, 56, 76, 83], except in one study [90]. When a very slow dose decrease rate (no more than 3 mg and 5% per week) is used, there is no difference [20, 23, 76] or only a slight difference [56] for this variable between patients who become and remain drug-free and patients who do not. A comparative study by Senay et al. [83] has clearly shown that a rapid withdrawal (10% per week) was correlated to more drop-outs, drug-resuming or study interruption than a gradual withdrawal (3% per week). Recently, Kanof et al. [47] described in detail the mood change, their relations to the other withdrawal symptoms and their relationship with the difficulty to reach the zero-methadone dose in a with-

drawal regimen of 5 mg and then 3 mg per week decrements. Payte and Khuri [71] suggest that dose reduction should be less than 10% of the established tolerance or maintenance dose and that there should be 10–14-day intervals between dose reductions.

Interaction between outcome indicators during treatment

This part of the paper deals with some truisms concerning interactions between the different indicators of outcomes; truisms which are worth knowing.

Breakdown with addicts milieu is not a moral goal but a pragmatic necessity: to live with an addict [45] or to have substance users in the social network [34] is related to poor outcomes.

Having a job during MMT is often [21, 26, 41, 46] but not systematically [32, 34, 83] associated with better outcomes. Good clinical attendance and no methadone dose missing are the patients' behavior variables correlated to improvement [2].

It is clearly established that the lower the heroin use during MMT before detoxification, the higher is the probability of remaining narcotic-free after methadone detoxification [2, 26, 45, 56, 57, 73].

Abuse of none opiate drugs, such as benzodiazepines, marijuana [18], and alcohol [8, 26, 45] during MMT are related to poorer outcomes. It is worth noting that some studies found that alcoholism results in poorer outcomes per se and not through an association with narcotic use persistence or relapse [21, 28]. Ball and Ross [2] report a similar phenomenon: cocaine use during MMT is associated with cocaine use persistence.

Finally, retention in treatment has to be borne in mind as an indicator for its interactions with the others indicators (heroin use cessation, criminality reduction, HIV prevention). We have already outlined the favorable influence of length of treatment on the indicators: even if there is a correlation between short-term abstinence after admission and long-term abstinence during MMT [2], some patients need 1, 2, 3 or more years to become abstinent and stop illicit behaviors. On the other hand, daily narcotic use is moderately correlated with drop-outs [41].

Conclusion

MMT happens to have a real, although not total, efficiency to reduce illegal opiate abuse (and to some extent non-opiate drug abuse), criminality, morbidity and mortality risks among addicted people. A minority of patients (perhaps 5–20%) stay on MMT for a very long time (more than 10 years). Results are not homogeneous and efficacy ranges from a low to a high level. This heterogeneity is only weakly related to the patients' characteristics. We have seen moderately better results for older patients (older than 25 years), with shorter addiction careers and less past criminality. The negative influence of psychiatric comorbidity on MMT results is highly probable and has been

clearly established for anti-social personality disorders. In no case do these variables play a sufficient role to offer a rationale to select patients. The question of indication for patients below 20 years of age remains unanswered and would need longer development to consider all of its aspects. This is beyond the scope of this paper. In fact, this heterogeneity of results is mainly related to differences of functioning between MMPs and not to patients' characteristics as well demonstrated by the Ball and Ross study [2]. For instance, in their study, the rate of current intravenous users (with at least one intravenous drug intake in the preceding month) varies among programmes in a range of 1 to 6 (from 10 to 57%). From this and other work, it can be seen that poorer outcomes are obtained when there is restriction of methadone daily dose, low-quality medical and psychosocial services and some other functioning characteristics linked to a rather controlling and administrative approach than one which is empathic and supportive of the patients. The same items influence the ability of the MMPs to keep their patients in treatment and to allow them time for progression. The duration of treatment is related to the success, even if 1–4 years are sometimes needed to achieve it. Having a high retention rate should be an important objective of MMPs, particularly as concerns HIV infection risks. When this is the aim, high retention rates may be obtained [25]. It needs to do without a punitive and a confrontational style of therapeutic relation [108]: "We hold the bottle, you do as we say". There is no justification for delaying or [71] making access to an MMT difficult [19, 74]. Stopping methadone may only be considered for well-stabilized patients with a protracted abstinence from heroin and others drugs [71]. Dose decrease needs to be very slow [82] and methadone stopping needs to be well accompanied, for instance, with self-help group participation [103, 108]. If a patient wishes to remain in treatment, it is wise to continue treatment [71]. A not well-determined proportion of patients remains to treatment for a very long, even lifelong basis. Is this a failure? Many North American authors today give a negative answer to this question: "It is very important to make a distinction between dependence and addiction. A person can regularly take a dependence-producing substance without manifesting the distinguishing characteristics of addiction: compulsion, loss of control and continue use despite adverse consequences" [62] or "It is unfortunate that the success of MMT continues to be judged by what happens once it is discontinued" [108]. Available data imply that long-term methadone maintenance is medically safe [50]. For patients stabilized and treated on a long-term basis, their treatment may be organized in a medical maintenance model, leaving more counselling time for subjects starting treatment or needing intensified efforts [108].

In fact, we still know little on the neurobiology of opiate addiction and there may be long-term drug-induced alteration of the neurochemistry, possibly associated with an underlying genetic predisposition or vulnerability to addiction after initial exposure to opiates [50]. A recent work on Vietnam veterans [77] provides food for thought.

Long-term mortality rates of 20–30% among opiate addicts [39] have to be considered, in association with the ability of MMT to reduce mortality, when we discuss the question of a minority of patients needing very long-term MMT.

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