

## When “enough” is still not “enough”. Effectiveness of high-dose methadone in the treatment of heroin addiction

Icro Maremmani <sup>1,2,3</sup>, Matteo Pacini <sup>1,3</sup>, Sonia Lubrano<sup>1</sup>,  
Mercedes Lovrecic <sup>1,4</sup>

### *Summary*

In the long-standing diatribe about methadone maintenance, Dole & Nyswander were the first to support the practice of standard methadone treatment with dosages above 100 mg/day. However, several clinicians persisted in their view that lower dosages could provide most patients with significant improvement. Data from the literature strongly support the evidence that 100 mg-maintenance is more effective than that with 50 mg- in treating opiate abuse during the first 5-10 months of treatment. High dosages can be useful, bringing special benefits to patients whose opiate use has proved to be particularly resistant to treatment. Higher dosages may be used where there is a concurrent psychopathology, persistent opiate use or symptoms of incomplete coverage by methadone. Dosages above 100 mg/die, seem to give the best results. Therefore there is no scientific justification for boycotting the use of dosages between 80 and 120 mg/day .

Key words: Methadone Treatment - High dosages

### **Introduction**

As long as the late sixties, researchers at Rockefeller University, in New York, USA, started to discard the psychological theories of opiate addiction that had been put forward up to that point. Those theories had portrayed opiate addiction as being due to psychological attitudes expressed by addicts themselves through substance use. In line with that view, therapeutic programmes were developed which aimed at psychosocial readjustment after a brief detoxification phase. On the other hand, Dole & Nyswander

---

Address for reprints: Icro Maremmani, MD; Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies - University of Pisa, Via Roma 67 - 56100 Pisa - Italy

<sup>[14]</sup> had just put forward the suggestion that heroin addiction may actually be a metabolic disease. Since then, clinical studies and laboratory evidence have been consistent with each other in showing that relapses into heroin use, elicited by the craving for the substance, are nothing but a dysfunction of the endogenous opioid system which develops as a consequence of prolonged opiate use. Although some patients may lead a stably normal life in a drug-free condition after accomplishing a short-term therapeutic program, most former drug-users are, with a high degree of probability, destined to experiences craving that may increase as time goes by. Craving can be described as an overwhelming urge to take heroin, as long as the latter is perceiving as being available. It elicits symptoms of neurovegetative excitement, drives the subjects' behaviour as to find the substance, and makes them incapable of suppressing or deferring their urge, despite any obstacles and/or predictable jeopardizing of the their own social integration. Eventually, severe social maladjustment is the inevitable outcome <sup>[43]</sup>. If such subjects are not promptly enrolled in a methadone treatment programme, they can be expected to relapse into heroin use, even if they have the strongest possible motivation to maintain a heroin-free condition and avoid losing whatever social status they had acquired during initial treatment. In other cases, methadone treatment aims to normalize the opioid functioning of the patient <sup>[11; 29; 30]</sup>.

Dr. Kreek examined patients who had been detoxified from heroin or had tapered methadone, in a spontaneously enduring condition of abstinence, and discovered neuroendocrine abnormalities in both groups. This finding led authors to hypothesize that abnormal endocrine reactivity may be a marker of the likelihood of relapse into heroin use <sup>[32; 33]</sup>. New investigation techniques and the later discovery of specific ligands for opioid receptors became a source of new interest in what is now called protracted withdrawal syndrome <sup>[12]</sup>.

Methadone treatment is currently the best treatment for opiate addiction, as far as the prevention of relapses into heroin use is concerned. However, a methadone maintenance treatment programme (MMTP) must follow precise technical paths in order to achieve its pursued objectives. A selection of subjects for whom treatment is suitable should be performed first. Then, the withdrawal-related anxiety of street addicts must be quickly buffered and, soon afterwards, a condition of opioid blockade must be achieved in order to prevent the effects of any further heroin injections. Eventually, the condition of craving must be gradually guided towards extinction. The accomplishment of these goals required the correct utilization of methadone itself, especially as far as the administration of adequate dosages is concerned. Technically speaking, MMTP moves through different stages: the induction stage consists in reaching the subject's tolerance threshold so as to buffer withdrawal symptoms; at the end of this phase, dosages are gradually increased above the initial level (e.g. 20 mg/day) in order to increase the subject's tolerance to a level that provides protection against possible heroin overdosing. During the next phase, stabilization, dosages are further increased until a level is reached which is high enough to maintain morphine-negativity at urinalysis. The stabilization dosage is then maintained, though dose variations may be needed during treatment, and attention should be given to the question of social rehabilitation. Once patients have

achieved full and stable social adjustment, but only then, can tapering be taken into consideration. Any tapering phase will be accomplished in a drug-free condition (dose zero), as long as no regression along the rehabilitative path is observed, let alone any relapse into heroin use. In those cases tapering should be performed slowly enough to allow clinicians to observe possible changes.

Opiate blockade is likely to be reached at a dosage ranging between 80 and 120 mg/day. This range was determined in the first double-blind trials performed by Dole, Nyswander and Kreek at the Rockefeller University back in 1966. Patients were treated for four weeks with different opiates (heroin, morphine, dilaudid©, methadone and saline as placebo) with respect to different standard levels of pharmacological stabilization and opioid tolerance: no euphoric effects followed the administration of any opiate drug for patients stably treated with 80-120 mg/day methadone. The existence of an opioid blockade was confirmed in samples taken from street heroin addicts <sup>[15]</sup>.

Only after several years of studies on large samples was the clinical significance of these observations wholly understood. Over time, studies have shown that methadone dosages higher than 80 mg/day are correlated with a higher grade of psychosocial rehabilitation.

## **Review of the studies**

### ***Jaffe, 1970***

This is a double-blind study comparing patients treated with high vs. low dosages. 63 subjects were randomized into two groups: 32 patients treated with low doses (on average 32 mg/day) and 31 treated with higher doses (100mg/die, reached within seven weeks). The variables taken into consideration comprise retention rate, use of opiates as assessed by urinalyses, and work adjustment. Urinalyses were performed twice or three times a week. The retention rate at 14 weeks was 58% for the high dose group, and 50% for the low dose subjects. The number of unemployed patients at study entrance who found a job during treatment tended to be higher among high dose patients, though without statistical significance <sup>[26]</sup>.

### ***Perkins and Bloch, 1970***

This retrospective study on as many as 521 patients shows a positive correlation between methadone dosage (above or below 80 mg/day) and retention in treatment <sup>[45]</sup>. Subjects treated with higher dosages tend to stay in treatment longer.

### ***Goldstein, 1970; 1971; 1972a; 1972b***

All four studies report the results of a single-blind trial, comparing dosages of 30, 50 and 100 mg for newcomers to a methadone maintenance programme. Subjects were started on 30 mg/day and had their dosage increased by 10 mg a day to the dosage that had been decided. In the 1970 report, Goldstein describes the results through the first three months for a total of 206 subjects, 20 receiving 30 mg, 80 50 mg and the other 106 100 mg. To quote the author: “as it emerges from urinalyses and standardized interviews, subjects receiving 100 mg take less to achieve abstinence from heroin use than peers receiving lower dosages”. Later, in 1971, Jaffe mentions a comparison study

considering dosages of 30, 50, 80 and 100 mg, together with other data from 200 mg-treated subjects, though these have not yet been reported. In an oral presentation at the 4th National Conference on methadone treatment (held in 1972) he explained that “a group of patients” went on to enter a second double-blind trial, in which dosages were increased from 50 up to 100 mg, and then to 250 mg, and in some cases decreased to 80 mg, across a 35-week time-span. “Apart from the predictably slow change [...] no side effect or street opiate use detectable by urinalysis was observed for higher dosages”. The conclusion was that a rapid dose increase is effective not only on possible symptoms, but on opiate use, too <sup>[17-20]</sup>.

***Berry, 1972***

This study evaluated different methadone dosages (30, 50 or 100 mg) in 200 patients assigned to different groups according to their addiction history, trouble with the law, and environmental and working conditions. Study duration was 4 months. Evaluation accounted for the retention rate, the use of street opiates during treatment, number of legal questions and social adjustment. At the end of the study no differences were found in any of the variables between the three groups. Retention rates and opiate use recurrence rate were quite similar. Values were 56%, 54% and 60%, for the low-dose, intermediate-dose and high-dose groups, respectively. Opiate use was infrequent as a trend (12%, 17% and 12%). Authors conclude that patients were likely to have been enrolled in the dosage-group that was suitable for the severity of their condition, so that dosages proved to have been adequate. Another acceptable observation is that dropouts may have been precisely those for whom assigned dosages were not adequate <sup>[3]</sup>.

***Brown et al., 1972***

Authors looked into the relationship between methadone dosages and treatment outcome. 273 subjects were divided into two dosage groups, those above (n=207) and below (n=66) 60 mg. The variables considered were 15-month retention rate, use of opiates as ascertained by urinalyses and social adjustment. Higher-dose patients showed a retention rate of 61%, against 23% for low-dosage ones (p<.01) <sup>[6]</sup>.

***Garbutt and Goldstein, 1972***

Garbutt & Goldstein (1972) performed a single-blind comparison between patients treated with 30, 50 or 100 mg/day methadone. 30 mg patients continued with the starting dosages throughout the study. 50 mg peers increased their dosages by 10 mg on the third and again on the fifth day. 100 mg subjects did not change dosages after the fifteenth day. As many as 180 subjects were enrolled, and study lasted three months. Variables considered were retention rate, opiate abuse as shown by urinalyses and self-evaluated discomfort. At the end of 13 weeks, a significant difference emerged between 50 mg-treated subjects and 100 mg-ones (p<.05); the latter were more likely to be retained. After 27 weeks, the 50 mg groups showed a higher retention rate than the 30 mg one (p<.05) <sup>[16]</sup>.

***Berry and Kuhn, 1973***

In this double-blind randomized trial, 52 patients, who had been stabilized with 100 mg/day and had been in treatment for an average of 10 months, were matched on

the basis of treatment duration at time of evaluation. Dosages were decreased for one member of each group by 10 mg every four weeks, down to a 50 mg level. Matched peers were maintained on 100 mg. The variables studied were retention rates, reasons for dropping out, opiate use shown by urinalyses, legal and familial status, social adjustment, clinical features and medical problems. The twenty-week retention rate was 65% (16/26) in the decreasing dose group, and 69% (17/26) among control peers. Opiate abuse did not differ between the two groups, nor did any other statistically significant differences emerged from the variables considered <sup>[4]</sup>.

***Bowling et al., 1973***

131 patients, comprising 57 treated with at least 140 mg/day, and 74 with 70 or 80 mg/die were compared in terms of opiate abuse recurrence, use of non-opioid drugs and social adjustment. No differences emerged between the two groups. Average retention in treatment was 22.6 mos. for the high dose subjects, compared with 12.9 months for the low dose ones. There was a positive correlation between dosage and time spent in treatment: higher dose-treated subjects tended to stay in treatment longer <sup>[5]</sup>.

***Goldstein and Judson, 1973***

Goldstein and Judson provided a good example of a single-blind randomized trial. Results obtained with doses of 40, 80 and 160 mg/day were compared for subjects who had been maintained on 80 mg/day for as long as the previous nine weeks. From the tenth week on, for the next seven weeks, group dosages were increased by 10 mg/week, or decreased by 5 mg, or maintained. Patients in each group then received stable treatment at their latest dose levels, for as long as 18 weeks.

The variables considered comprised retention rate, reasons for dropping out, opiate abuse as ascertained by urinalyses, and symptoms investigated through a 45-item questionnaire, administered at the end of one week, nine-weeks and 27-weeks. All patients attended the outpatient centre twice a day, half of them receiving split doses, the other half a single dose and a placebo, following a single-blind randomized schedule.

120 subjects were randomized at study entrance, 40 for each group, but a total of 17 dropped out in the early stable-dose phase. Survival tables show significant differences between retention rates: these were 45% (15/33, between week 9 and 27) for the 40 mg group, 71% (25/35) for the 80 mg one, and 74% (26/35) for the 160 mg <sup>[22]</sup>.

***Goldstein et al., 1975***

Authors evaluated the consequences of methadone dose increases in response to patients' requests, so making it possible to assess the relationship between behavioural changes and self-decided methadone increases. Patients were allowed to increase or decrease their dosage by 5 mg, once or more a week. An upper threshold of 120 mg/day was fixed. Subjects who asked to raise their dosage (n=18) achieved a statistically significant and worthwhile fall in illicit opioid use <sup>[21]</sup>.

***Handal and Lander, 1976***

For 155 methadone-maintained patients, higher methadone doses accounted for lower rates of ongoing street-opiate use <sup>[23]</sup>.

***Ling et al., 1976***

Authors performed a double-blind comparison within a sample of 430 heroin addicts divided into three groups: patients received either LAAM or methadone, the latter at two different fixed dosages. 30 mg/day methadone were administered for one week, after which their dose was increased by 10 mg/day up to a maintenance dose of either 50 or 100 mg/day. Treatment duration was 40 weeks.

Variables considered were retention rates, substance abuse, a series of self-evaluated symptoms, reasons for dropping out, and a variety of features indicating the level of treatment safety. Only subjects, who had been in treatment for at least 50 days were admitted.

LAAM-treated subjects showed an outcome intermediate between high dose (100 mg/day) and low dose (50 mg/day) methadone ones. Significant differences ( $p < .05$ ) were found for ongoing opiate abuse (more frequent among low dose subjects) and global clinical judgment (better for the high dose group). 40-week retention was similar between groups (42% for 50 mg vs. 52% for 100 mg), as was subjective well-being<sup>[38]</sup>.

***Siassi et al., 1977***

Authors examined the relationships between methadone dosages and non-opioid abuse in 266 subjects who had been on maintenance for at least two years. 27 subjects were treated with less than 60 mg (48 mg on average) and 19 received more than 80 mg (86 mg on average), while average dosage treated-subjects ( $n=46$ ) were left out of consideration. The two studied groups showed similar anagraphical, environmental, social and toxicological features. Opiate and amphetamine use both had similar frequencies. On the other hand, low dose subjects tended to resort to sedatives: several of these patients tested positive for benzodiazepines and barbiturates, and displayed higher levels of alcohol consumption<sup>[47]</sup>.

***Siassi et al., 1977***

Authors analysed data gathered from 144 patients, who had been in treatment for at least 21 days but then dropped-out, staying continuously out of treatment for at least 2 years. Subjects were grouped in three populations (low, intermediate and high dosage). 28 subjects who received intermediate dosages (between 60 and 80 mg) were not considered within the analysis, which comprised only the 33 low dose subjects (48 mg on average) and the 53 high dose subjects (86 mg on average). A positive outcome was defined by a stable working and social adjustment (continuously for three months), no ongoing substance use, no criminal activity and spontaneous tapering. 73% high dose patients achieved that favourable outcome, vs. 30% among low dose peers ( $p < .001$ ). As in other similar studies, higher dosages resulted in longer treatment duration (748 days vs. 393 on average)<sup>[46]</sup>.

***Havassy et al., 1979***

This was an open-label trial using flexible doses. 116 methadone-maintained subjects belonging to two different centres were grouped in three different treatment groups: flexible dose with a reward after dose decrease (allowance of more frequent or larger take-home), flexible dose with neutral feedback (neither disapproval nor reward), and

non-flexible standard treatment. Opiate abuse and course of dosages were taken into consideration. In another centre, subjects who had been started on 46-65 mg had their dosage increased (by an average of 20 mg over a six-week period), after which it was tapered back down to the starting level during the next 16 weeks. This fourth group displayed the lowest rate of substance abuse <sup>[25]</sup>.

***Stitzer et al., 1979***

23 patients maintained on 20 mg/day were given six chances to increase or decrease their daily dosage. Authors aimed to evaluate dose-related subjective changes or abuse behaviours. No individual changes emerged for those who chose to raise their dosage <sup>[49]</sup>.

***Craig, 1980***

This study evaluated a group of heroin addicts, apparently showing that 30 mg-treated subjects achieve as favourable an outcome as that of higher dose-treated peers. However, that result seems to be combined with a particularly low overall retention rate (10% at 12 months, which dwindled to even less during a further 12-month period) <sup>[8]</sup>.

***Ling et al., 1980***

68 subjects who had undergone a trial at Sepulveda VA Hospital were enrolled in a further study to investigate the effects of dose changes up to fixed values of either 50 or 100 mg/day along a double-blind randomized schedule. Staff members and patients decided together which dose would be adequate for the following six weeks, but they stayed blind to which dose had been administered to whom that far. Two-thirds of the patients, who had previously been receiving 50 mg, asked to have their dosage increased to over 60 mg <sup>[37]</sup>.

***McGlothlin and Anglin, 1981***

This study discusses the results of a 6-7 year follow up, based on data collected between 1971 and 1973 in three methadone maintenance treatment programmes, two of which received high doses, and the third lower doses over a limited period. The third group had unsatisfying results <sup>[44]</sup>.

***Hartel et al., 1988***

Hartel and colleagues analysed data from 190,000 urinalyses on 2,400 long-term (over 15 years) methadone-maintained patients in New York (the Bronx), between 1972 and 1988. Taking 70 mg/day as a threshold, it was demonstrated that higher dose-treated patients tended to stay longer in treatment, and that they used heroin and other substances, such as cocaine, less frequently, and had a lower incidence of HIV infection and AIDS. In patients treated with dosages above 80 mg, that effectiveness is clearly enhanced, especially in terms of reduced likelihood of HIV seroconversion <sup>[24]</sup>.

***Ball & Ross, 1991***

This 1991 study (comprising 5 methadone programmes in Baltimore, New York and Philadelphia) showed that heroin injectors reduced substance use by 71% after enrolment in a long-term methadone maintenance programme. What is even more striking is that 407 patients observed for one month appeared to reduce heroin use by a rate that was positively correlated with the methadone dosage administered: the higher the dosage,

the lower the frequency of heroin use. 27.9% of the 240 patients receiving less than 40 mg went on using heroin. Conversely, only 5.4% of the 203 treated with dosages over 45 mg continued heroin use. Lastly, no persisting heroin use was documented for patients taking over 75 mg/day <sup>[2]</sup>.

***Appel (cited by Joseph and Appel)***

Appel's review of 44 studies on methadone maintenance for the NIDA shows that dosage is the most reliable predictor of treatment retention: the higher the dose, the longer the time spent in treatment <sup>[1:28]</sup>.

***Caplehorn & Bell, 1991***

Caplehorn and Bell were able to confirm that methadone dose is an important predictor of treatment retention. Referring to three distinct dose levels (60 mg; between 60 and 80 mg/day; above 80 mg) authors showed that patients receiving over 80 mg/day had a higher retention rate. Notably, working adjustment, education, and involvement in crime affected treatment retention to a lesser degree than dosage <sup>[7]</sup>.

***D'Aunno & Vaughan, 1992***

The study refers to an analysis of a USA nationwide randomized sample drawn from 172 centres, with an average rate of success of about 70%. Authors point out that, in about half of the centres, patients were pushed to enter detoxification schedules within the first six months of treatment. 68% of programmes seemed to work within a 50 mg threshold, that is, below the value recommended by the GAO. Even within that threshold, higher dosages led to longer retention. When patients were allowed to decide on their dosages, and take-home facilities were accessible, the outcome (evaluated in terms of duration of treatment and abstinence from street opiate use) was far better. Authors note that, in terms of treatment philosophy, a radical change is needed in planning programmes, in which undermedication is the rule, and no account is taken for patients' requests in determining daily dose values. Moreover, the programmes, which comprised a majority of Afro-American patients, young addicts or unemployed junkies were particularly likely to keep their patients undermedicated, and often practice detoxification at an unreasonably early stage <sup>[9]</sup>.

***Strain et al., 1993***

This work mainly aimed to compare the effectiveness of low-to-moderate methadone dosages in a placebo-controlled double-blind randomized trial. The sample consisted of 247 cocaine-abusing heroin addicts. Methadone administered to patients for five weeks and then stabilized at 50, 20 or 0 mg/day for the following 15 weeks. Retention in treatment and use of illicit substances were both evaluated. Results showed a dose-effect correlation: higher doses did bring some advantages over placebo in terms of treatment retention, but had no influence on substance use <sup>[51]</sup>.

***Maddox et al., 1997***

Maddox and colleagues performed a one-year follow up on 610 heroin addicts, aiming to evaluate the relationship between methadone doses and a few other variables, which are already known to influence the outcome of methadone programmes. Methadone dosage was flexible and patients' requests for dose variations did weigh on

the decision taken. Average dosages administered ranged between 10 and 110 mg/day. Treatment retention was significantly affected by doses, higher ones being correlated with higher retention. Higher methadone dosages were also correlated with positive urinalyses for cocaine, while no relation was found with positivity for heroin <sup>[39]</sup>.

***Maxwell & Shinderman, 1999***

High methadone dosages improve patients' outcome <sup>[42]</sup>. Maxwell & Shinderman from the “Centre for Addictive Problems” in Chicago enrolled 164 incontinent patients in a special group treated with dosages above 100 mg (ranging between 780 mg/day and 110 mg/day, 211 mg/day on average). Patients in treatment at the same centre usually received an average dosage of 65 mg/day. High-dose patients reduced heroin use as ascertained by urinalyses by 97% (87% vs. 3% p<.001). The likelihood of ongoing heroin use was 67% for patients receiving standard dosages (55% vs. 37%). For 63% of the incontinent patients treated with high dosages a concurrent psychiatric disorder was assessable, versus 32% among standard patients. Treatment outcome for dually diagnosed patients improved significantly for those belonging to the high-dose group. Authors point out that dosages above 100 mg/day are not only safe, but are actually required to prevent illicit opiate use, stabilize symptoms of psychopathology and reduce alcohol and benzodiazepine use.

***Strain et al., 1999***

High methadone dosages proved to be “more effective than low ones”: this statement was published in a 1999 JAMA issue. According to Strain and colleagues, working at the Johns Hopkins University School of Medicine in Baltimore, Maryland, higher methadone dosages are not just safer for heroin addicts going through the maintenance phase, but may also be helpful to them in achieving a better level of social adjustment. That is what emerged from a 40-week trial on 192 patients. Researchers noted how methadone clinicians usually administer dosages ranging between 30 and 60 mg/day. Authors regard dosages of 40-50 mg as low, and 80-100 mg as high. All patients were able to request counselling facilities. Although opiate use was documented within both groups, authors found that subjects receiving high dosages showed a greater trend towards dwindling use of street opiates. Authors conclude that 40-50 mg lead to a significantly positive outcome. Their most important finding, on therapeutic grounds, is that methadone treatment ranging between low and high dosages can be expected to grant patients significant psychosocial improvement <sup>[50]</sup>.

Speaking at the National Institute on Drug Abuse, director Alan Leshner stated that “heroin addicts treated by methadone show a better outcome in respect of patients that receive no methadone treatment”. Moreover, integrated programmes, by providing behavioural and pharmacological interventions within the same setting, give patients the best results. Several studies have reported the superiority of high methadone dosages such as those used in this study; dosages above 100 mg/die have shown they are the most appropriate for most patients <sup>[36]</sup>.

***Maremmani et al., 2000***

90 methadone-maintained heroin addicts, comprising 38 with at least one further mental disorder, and 52 with no psychiatric comorbidity, were studied in order to de-

termine whether any relationship could be assessed between stabilization dosages and treatment retention. Dually diagnosed patients needed an average stabilization dosage of  $154 \pm 84$  mg/day, whereas an average  $99 \pm 49$  mg/day was required for uncomplicated peers. Over a 990-day period no differences were found in treatment retention <sup>[40]</sup>.

***Johnson et al., 2000***

220 patients treated with dosages ranging between 60 and 100 mg/day (n=55), or 20 mg/die (n=55) were compared, over a 17-week period, with 55 patients receiving LAAM (75-115 mg/day) and 55 receiving buprenorphine (16-32 mg/die). Dosages were flexible for all groups, except for the 20 mg methadone one. Patients treated with higher dosages showed a higher retention rate, attended the centre more regularly, had a low rate of opiate use and stayed abstinent for longer periods (of at least  $\geq 12$  weeks for 28%) <sup>[27]</sup>.

**Discussion**

If methadone treatment was regarded in the same way as any other medical or pharmacological approach, there would not be such concern about what methadone dosage is adequate within maintenance treatment programmes for heroin addiction. In spite of the proven effectiveness of methadone therapy against drug-related crime, cultural and political issues have limited its use so far <sup>[48; 54]</sup>. On clinical grounds, it is important to warn physicians' that their therapeutic decisions should be made in full autonomy, and that they should act to prevent political pressure weighing upon clinical practice.

Speaking about the dose-related pharmacological effects of methadone, it should be determined whether dosages higher than those currently used are required to make therapeutic goals more easier to achieve for most heroin addicts. In addition, it can be stated that low dosages are certainly ineffective for a subgroup of patients.

In the traditional diatribe about methadone maintenance, Dole & Nyswander <sup>[10; 13; 14]</sup> were the first to support the practice of standard methadone treatment with dosages above 100 mg/day. However, several clinicians persisted in arguing that lower dosages would allow most patients to significantly improve their situation.

Ling and colleagues <sup>[38]</sup> provided convincing evidence that 100 mg-maintenance is more effective than 50 mg- in treating opiate abuse during the first 5-10 months of treatment. This finding does not mean that all patients need a 100 mg/day dosage, but it does imply that at least 10% of all patients would achieve the best results in a maintenance regimen by receiving more than 50 mg/day during the first 5-10 months of their programme. Later studies <sup>[4; 22; 26; 37]</sup> failed to discover any evidence against these findings by Ling and colleagues <sup>[38]</sup>.

Another randomized study, dealing with dosages above 100 mg/day, was that by Goldstein & Judson, who used fixed dosages of 40, 80 and 160 mg/day. Their results showed that high dosages can be useful, with special benefits achieved by patients whose opiate use had proved to be particularly resistant to treatment. Goldstein <sup>[19; 20]</sup> & Stitzer and colleagues <sup>[49]</sup> also suggested that a rapid, sharp increase in dosages may

produce a decisive impulse towards abstinence from opiate use, than that obtainable with a gradual increase.

However, the problem is not what the highest possible dosage is - it is far above 100 mg/day<sup>[40]</sup>, with an official maximum of 780 mg/day<sup>[42]</sup>. The real problem is that of assessing the lowest dose that is able to control the risk of relapse.

The standard use of a dose ranging between 20 and 40 mg, which has characterized Italian practice, and the widespread practice of keeping dosages as low as possible, in response to political pressures, raised two urgent issues. First, why boycott the use of dosages between 80 and 100 mg/day? Second, are dosages ranging between 20 and 40 mg/day really effective for all the patients who receive them? If it is true that 100 mg is more effective than 50, for at least one subgroup of patients, then it is simply consequential to add that a dose of 100 mg has a wider outreach and can achieve more than 40, 30 or 20 mg.

Some authors tried to draw comparisons between low dosages, between 30 and 50 mg. Garbutt & Goldstein<sup>[16]</sup> provided the most accurate results, showing no real advantage in prescribing 50 mg rather than 30 mg. Other studies<sup>[17-20]</sup> did not reach clear-cut conclusions. Berry's work<sup>[3]</sup> compared fixed dosages of 30, 50 and 100 mg/day chosen for patients with different degrees of severity; it showed a similar outcome for the three groups, suggesting that 30 mg should not be regarded as the best dosage for all kinds of patients, but only for those whose condition is least severe.

In conclusion, there is no evidence that low dosages are adequate for the vast majority of patients, and it is doubtful whether dosages of about 30 mg/die are enough to any of them.

This controversy could be resolved if significant differences between patients were accounted for when assigning dosage values. A few cases have been reported to document the phenomenon of an idiosyncratic methadone metabolism (e.g. Walton et al., 1978<sup>[53]</sup>). In reviewing the factors that have been shown to influence the pharmacological effectiveness of methadone, Kreek<sup>[31; 34]</sup> provides details about the pharmacological interactions and medical conditions that may interfere with the bio-availability of methadone. Lower dosages may then become suitable, if patients prefer them, while higher dosages may be used in cases of concurrent psychopathology, persistent use of opiates or symptoms of incomplete coverage by methadone. Treece & Nicholson<sup>[52]</sup>, adopting the DSM III diagnostic criteria, calculated an average dose of 87 mg/day for subjects (n=5) with schizoid, schizotypic abnormalities or odd personality disorders, who had been identified among a sample of 31 methadone-maintained patients. Nineteen patients displaying features of dramatic personality disorders required an average dose of 48 mg. Seven subjects with cluster C personality pictures required the lowest average dose (36 mg) (p<.001). Maremmani and colleagues showed that patients with psychopathological abnormalities at treatment entrance require a higher methadone dose to reach stabilization<sup>[41]</sup>. The same authors reported that the compliance with treatment of psychiatrically ill heroin addicts improved significantly when high dosages were used<sup>[40]</sup>.

In general, dosages above 80 mg/die seem to give the best results. As many as fourteen years ago, Dole had stated that “there are no reasons for us to limit our prescriptions according to some upper dose threshold, thus using dosages that only provide with partial improvement. As for antibiotics, cautiousness means to use dosages high enough to allow the best results to be achieved<sup>[11]</sup>”. On clinical grounds, patients often warn physicians saying “I don’t feel I am taking enough methadone” “I wake up at night with a craving for heroin”, or “When I wake up in the morning I already feel tired”. In such cases clinicians, if they accept the arguments of the present overview, should reject all reluctance to increase dosages above any preconceived threshold, that is grounded on the unreasonable view that it should already be enough<sup>[35]</sup>.

Looking forward to future research efforts, a crucial task will be that of assessing whether better criteria can be defined for matching the various categories of patients with the dosages that are best for them, whether these dosages are high or low.

## **References**

1. Appel P. Treatment issue report #56: Review of a NIDA grant. The relationship of treatment policy to client retention by Watters, J.A. and Price, R.H. Bureau of Research and Evaluation, University of Michigan. Unpublished internal report of the New York State Division of Substance Abuse Services.
2. Ball J., Ross A. (1991): Follow-up study of 105 patients who left treatment. In J. C. Ball, A. Ross Eds, *The Effectiveness of Methadone Maintenance Treatment*. Springer-Verlag, New York.
3. Berry G. J. (1972): Dose-related responses to methadone, including placebo therapy. *Proceedings of the fifth National Conference on Methadone Treatment*. National Association for the Prevention of Addiction to Narcotics, New York. pp. 409-410.
4. Berry G. J., Kuhn K. L. (1973): Dose related response to methadone: reduction of maintenance dose. In National Association for the Prevention of Addiction to Narcotics Ed., *Proceedings of the fifth National Conference on Methadone Treatment*. National Association for the Prevention of Addiction to Narcotics, New York. pp. 972-979.
5. Bowling C. E., Moffett A. D., Taylor W. J. (1973): High versus low dose maintenance therapy: An empirical test. In C. D. Chambers, L. Brill Eds, *Methadone: Experiences and Issues*. Behavioural Publications, New York. pp. 143-148.
6. Brown B. S., Dupon R. L., Bass U. F., Glendinning S. T., Koziel N. J., Meyers M. B. (1972): Impact of a multimodality treatment program for heroin addicts. *Comprehensive Psychiatry*. 13(4): 391-397.
7. Caplehorn J. R. M., Bell J. (1991): Methadone dosage and retention of patients in maintenance treatment. *The Medical Journal of Australia*. 154: 195-199.
8. Craig R. J. (1980): Effectiveness of low-dose methadone maintenance for the treatment of inner city heroin addicts. *International Journal of Addictions*. 15(5):

- 701-710.
9. D’Aunno T., Vaughn T. E. (1992): Variations in methadone treatment practices. *JAMA*. 267(2): 253-258.
  10. Dole V. P. (1965): In the course of professional practice. *N.Y.State J.Med.* 65: 927-931.
  11. Dole V.P. (1988): Implications of methadone maintenance for theories of narcotic addiction. *JAMA*. 260: 3025-3029.
  12. Dole V. P. (1994): What have we learned from three decades of methadone maintenance treatment. *Drug and Alcohol Review*. 13(3): 330-338.
  13. Dole V. P., Nyswander M. E. (1965): A medical treatment for diacetylmorphine (heroin) addiction: A clinical trial with methadone hydrochloride. *JAMA*. 193: 80-84.
  14. Dole V. P., Nyswander M. E. (1967): Heroin Addiction: A Metabolic Disease. *Archives of Internal Medicine*. 120: 19-24.
  15. Dole V. P., Nyswander M. E., Kreek M. J. (1966): Narcotic Blockade. *Archives of Internal Medicine*. 118: 304-309.
  16. Garbutt G. D., Goldstein A. (1972): Blind comparison of three methadone maintenance dosages in 180 patients. In *National Association for the Prevention of Addiction to Narcotics Ed., Proceedings of the fourth National Conference on Methadone Treatment*. National Association for the Prevention of Addiction to Narcotics, pp. 31-37.
  17. Goldstein A. (1970): Blind controlled dosage comparisons with methadone in 200 patients. *Proceeding of the Third National Conference on Methadone Treatment*. Public Health Service Publication N° 2172. U.S. Govt. Print. Off., Washington, DC. pp. 31-37.
  18. Goldstein A. (1971): Blind dosage comparison and other studies in a large methadone program. *Journal of Psychedelic Drugs*. 4(2): 177-181.
  19. Goldstein A. (1972): Blind comparison of once-daily and twice-daily dosage schedules in a methadone program. *Journal of Clinical Pharmacology and Therapeutics*. 13(1): 59-63.
  20. Goldstein A. (1972): Heroin addiction and the role of methadone in its treatment. *Archives of General Psychiatry*. 26(4): 291-297.
  21. Goldstein A., Hansteen R. W., Horns W. H. (1975): Control of methadone dosage by patients. *JAMA*. 234(7): 734-737.
  22. Goldstein A., Judson B. A. (1973): Efficacy and side effects of three widely different methadone doses. In *National Association for the Prevention of Addiction to Narcotics Ed., Proceeding of the fifth National Conference on Methadone Treatment*. National Association for the Prevention of Addiction to Narcotics, New York, NY. pp. 21-44.
  23. Handal P. J., Lander J. J. (1976): Methadone Treatment : program evaluation and dose response relationships. *International Journal of Addictions*. 11(3): 363-375.

24. Hartel D., Selwyn P. A., and Schoenbaum E. E. (1988): Methadone Maintenance treatment and reduced risk of AIDS and AIDS-specific mortality in intravenous drug users, Abstract N° 8546. Fourth International Conference on AIDS, Stockholm, Sweden.
25. Havassy B., Hargreaves W. A., De Barros L. (1979): Self regulation of dose in methadone maintenance with contingent privileges. *Addictive Behaviors*. 4: 31-38.
26. Jaffe J. H. (1970): Further experience with methadone in the treatment of narcotics users. *International Journal of Addictions*. 5(3): 375-389.
27. Johnson R. E., Chutuape M. A., Strain E. C., Walsh S. L., Stitzer M. L., Bigelow G. E. (2000): A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *New England Journal of Medicine*. 343(18): 1290-1297.
28. Joseph H., Appel P. (1993): Historical perspective and public health issues. In M. W. Parrino Ed., *State Methadone Treatment Guidelines*. U.S. Department of Health & Human Services, Rockville, MD. pp. 11-24.
29. Kreek M. J. (1973): Medical safety and side effects of methadone in tolerant individuals. *JAMA*. 223(6): 665-668.
30. Kreek M. J. (1978): Medical complications in methadone patients. *Annals of the New York Academy of Sciences*. 322: 110-134.
31. Kreek M. J. (1983): Health consequences associated with the use of methadone. In J. R. Cooper, F. Altman, B. S. Brown, D. Czechowicz Eds, *Research on the treatment of narcotic addiction. State of the art. Treatment Research Monograph Series*. NIDA, Rockville, Maryland. pp. 456-482.
32. Kreek M. J. (1986): Tolerance and dependence: Implications for the pharmacological treatment of addiction. In L. S. Harris Ed., *Problems of Drug Dependence*, 1986. NIDA Research Monograph 76. NIDA, Rockville, MD.
33. Kreek M. J. (1995): Pharmacological Treatment of Addiction: Normalization of Physiology and AIDS Risk Reduction. In A. Tagliamonte, I. Maremmani Eds, *Drug Addiction and Related Clinical Problems*. Springer Verlag, Wien New York. pp. 165-174.
34. Kreek M. J., Bencsath F. A., Fanizza A., Field F. H. (1983): Effects of liver disease on fecal excretion of methadone and its unconjugated metabolites in maintenance patients: Quantitation by direct probe chemical ionization mass spectrometry. *Biomedical Mass Spectrometry*. 10: 544-549.
35. Leavitt S. B., Shinderman M. S., Maxwell S., Eap C. B., Paris P. (2000): When "enough" is not enough: New perspectives on optimal Methadone Maintenance Dose. *Mount Sinai Journal of Medicine*. 67(5-6): 404-411.
36. Leavitt S. E. (1999): News and Updates. *Addiction Treatment Forum*. June, 1.
37. Ling W., Blakis M., Holmes E. D., Klett C. J., Carter W. E. (1980): Restabilization with methadone after methadyl acetate maintenance. *Archives of General Psychiatry*. 37(2): 194-196.
38. Ling W., Charuvastra C. V., Kaim S. C. (1976): Methadyl acetate and methadone

- as maintenance treatments for heroin addicts. *Archives of General Psychiatry*. 33: 709-700.
39. Maddux J. F., Prihoda T. J., Vogtsberger K. N. (1997): The relationship of methadone dose and other variables to outcomes of methadone maintenance. *American Journal on Addictions*. 6(3): 246-255.
  40. Maremmani I., Zolesi O., Aglietti M., Marini G., Tagliamonte A., Shinderman M. S., Maxwell S. (2000): Methadone Dose and Retention in Treatment of Heroin Addicts with Axis I Psychiatric Comorbidity. *Journal of Addictive Diseases*. 19(2): 29-41.
  41. Maremmani I., Zolesi O., Agueci T., Castrogiovanni P. (1993): Methadone Doses and Psychopathological Symptoms during Methadone Maintenance. *Journal of Psychoactive Drugs*. 25(3): 253-263.
  42. Maxwell S., Shinderman M. S. (1999): Optimizing Response to Methadone Maintenance Treatment: Use of Higher-Dose Methadone. *Journal of Psychoactive Drugs*. 31(2): 95-102.
  43. McCance-Katz E. F., Rainey P. M., Jatlow P., Friedland G. (1998): Methadone effect on zidovudine disposition (AIDS Clinical Trials Group 262). *Journal of Acquired Immune Deficiency Syndromes*. 15(18): 435-443.
  44. McGlothlin W. H., Anglin M. D. (1981): Long-term follow-up of clients of high- and low-dose methadone programs. *Archives of General Psychiatry*. 38: 1055-1063.
  45. Perkins M. E., Bloch H. I. (1970): Survey of a methadone maintenance treatment program. *American Journal of Psychiatry*. 126: 33-40.
  46. Siassi I., Angle B. P., Alston D. C. (1977): Comparison of the effect of high and low doses of methadone on treatment outcome. *International Journal of Addictions*. 12(8): 993-1005.
  47. Siassi I., Angle B. P., Alston D. C. (1977): Maintenance dosage as critical factor in methadone maintenance treatment. *British Journal of Addiction*. 72: 261-268.
  48. Smith T. A., Kronick R. F. (1979): The policy culture of drug: ritalin, methadone, and the control of deviant behaviour. *International Journal of Addictions*. 12: 943-946.
  49. Stitzer M., Bigelow G., Liebson I. (1979): Supplementary methadone self administration among methadone maintenance clients. *Addictive Behaviors*. 4: 61-66.
  50. Strain E. C., Bigelow G. E., Liebson I. A., Stitzer M. L. (1999): Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *JAMA*. 281 (11): 1000-1005.
  51. Strain E. C., Stitzer M. L., Liebson I. A., Bigelow G. E. (1993): Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine*. 119(1): 23-27.
  52. Treece C. D., Nicholson B. (1980): DSM III personality type and dose levels in methadone maintenance patients. *Journal of Nervous and Mental Disease*. 168:

- 621-628.
53. Walton R. G., Thornton T. L., Wahl G. F. (1978): Serum methadone as an aid in managing methadone maintenance patients. *International Journal of Addictions*. 13: 689-694.
54. Weppner R. S. (1979): Conflicting world views and the delivery of treatment to narcotics addicts: some socio-cultural observations. *Soc Sci Med*. 13: 257-262.

*Received September 20, 2002 - Accepted November 15, 2002*