Heroin Addiction and Related Clinical Problems

the official journal of

European Opiate Addiction Treatment Association
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The impact of methadone substitution therapy (MST) on illicit drug use and drug abuse-related quality of life: A European Study

Hamid Ghodse, Carmel Clancy, Adenekan Oyefeso (UK), Clemens Rösinger & Thomas Finkbeiner (Germany), Fabrizio Schifano & Giovanni Forza (Italy), Børge Sommer, Kate Runge Nielson & Jette Schodt (Denmark), Sylvie Wieviorka & Claude Gionnet (France), John O’Connor (Ireland), Laura Tidone & Marco Riglietta (Italy), Iduino Lopes (Portugal), Marta Torrens, Luis San, Marino Montes & Covadonga Rodriguez Copez (Spain)

Summary

Context: Although methadone substitution therapy (MST) is one of the most commonly used treatments for opiate dependence, legitimate questions continue to be raised about its effectiveness. Objective: To evaluate the impact of MST on illicit drug use and drug abuse-related quality of life (QoL). Design: Multicentre, cross-sectional case control study. Setting: Eleven MST programmes in eight European countries. Participants: Heroin dependent patients in MST programmes. Main outcome measures: Data on illicit drug use in the last month and injecting behaviour was extracted from the patient’s substance use profile derived from EuroSUD as part of intake and ongoing assessment. The Brief Addiction Recovery Status Scale (EuroSAAQ-BARSS). Results: In Treatment (IT) groups reported a significantly lower number of illicit drugs used in the last month than controls (IT1: t = -6.81, p < .00001; IT2: t = -7.61, p < .00001; IT3: t = -6.32, p < .00001; IT4: t = -10.14, p < .00001). IT patients reported significantly lower rates of injecting than controls IT1 (OR = 0.48, 95% CI = 0.24, 0.95), IT2 (OR = 0.21, 95% CI = 0.12, 0.37), IT3 (OR = 0.43, 95% CI = 0.22, 0.87) and IT4 (OR = 0.27, 95% CI = 0.13, 0.57). They also expressed better drug-abuse related QoL for those patients who had been in treatment for at least 7 months (IT2: t = 4.43, p < .00001; IT3: t = 4.52, p < .00001; IT4: t = 6.22, p < .00001). Furthermore, there was a consistently positive relationship between duration in treatment and...
QoL scores. **Conclusions:** MST impacts positively on illicit drug use, injecting and drug abuse-related QoL. MST has been demonstrated as a culture-free and

**Introduction**

Since its introduction in the 1960s methadone substitution therapy (MST) has become the most commonly used treatment for opiate dependence. Consequently, it has generated legitimate questions about its effectiveness. Although there are numerous demonstrable benefits, there are still concerns about the ability of methadone to foster continued dependency and sustain illicit drug use. There are also problems about its abuse liability and ease of diversion to the illicit market. More recently, concerns about health care costs associated with MST programmes seem to have increased globally, together with critical attention directed to their effectiveness. However, cost effectiveness can not be easily evaluated without explicit demonstration of the impact of MST on problematic opiate use, addiction-related problems and patients’ overall functionality and quality of life. These expectations apply not only to MST but also to all substance use treatment programmes. Most studies have focused on the impact of MST on illicit opiate use with little attention dedicated to the aspect of quality of life. Consequently the European Collaborating Centres in Addiction Studies (ECCAS) undertook a multicentre transnational study to evaluate MST under the following impact domains: reduction in illicit drug use and drug abuse-related quality of life (QoL).

A transnational study had become necessary in view of limited transcultural evidence about the impact of MST. Many outcome studies, mostly North American and Australian, though extensive, have been nationally focused, with limited geographical generalizability. Therefore the main objective of this study was as follows: to examine the impact of MST on illicit drug use, and drug abuse-related QoL in eleven MST programmes across eight European countries.

This study was designed out of the need to address the potential problems related to patient care and management provoked by the increasing cross-border mobility of opiate addicts in Europe. Furthermore, with an increasing tendency for clinicians to favour a European Union (EU) wide standard of good clinical practice, it was necessary to determine the threshold of the utility of MST across Europe.

The study hypotheses were as follows:

1. Opiate users already receiving MST, i.e. in-treatment (IT) patients, would report a significantly lower number of illicit drugs used, and a lower rate of illicit opiate use, in the last month than newly admitted patients (controls).
2. IT patients would report lower rates of injecting than controls.
3. IT patients would report a better drug abuse-related quality of life (QoL) than controls.
Material and Methods

Participants

Eleven centres offering Methadone Substitution Therapy (MST) programmes were recruited via the European Collaborating Centres in Addiction Studies (ECCAS) network, located in a total of eight European countries. Participating centres collaborated on the basis that their MST programmes shared similar characteristics in the following areas: treatment setting, staff composition, eligibility criteria for admission, assessment process, dosing and dispensing policies, and monitoring of treatment. Consequently the MST programme had an outpatient setting staffed by multidisciplinary personnel (i.e. psychiatrists, nurses, social workers and psychologists), the primary requirement for admission being physical dependence on opiates substantiated through the patient’s history of drug use, medical examination and positive urine test for opiates. Methadone was dispensed daily and in liquid form, and the treatment team formally reviewed patients’ status on a regular basis.

Patients attending each centre for methadone substitution therapy (MST) were eligible for recruitment into the study if they fulfilled the DSM III-R criteria for opiate dependence and had no clinical evidence of functional psychosis, schizophrenia or other psychotic disorders, or major neuropsychiatric syndromes. Participating centres recruited subjects consecutively over a period of six to eighteen months according to patient availability and study criteria. Ethical approval was obtained at each centre and patients’ informed consent was obtained. The overall sample size was 673.

Design

This was a case control study. The control group included current patients who were new to treatment (i.e. had never been in treatment before or had been out of treatment for a minimum of 3 months) and patients who had been in treatment for one month or less (i.e. stabilization period). “Cases” were current patients who had been in treatment (IT) for at least 2 months preceding the start of the study. The in-treatment (IT) group was further classified according to length in treatment, resulting in four IT groups, as follows: IT1 were those who had spent 2-6 months in treatment; IT2, 7-18 months; IT3, 19-36 months and IT4, 37 months and over. The main criterion variables in this study were number of illicit drugs used in the last month, illicit opiate use; injecting in the last month and drug abuse-related quality of life (QoL). The main predictor was involvement in treatment.

Classification into multiple treatment groups was undertaken to evaluate the difference between new patients (control) and all IT patients on impact criteria.

Assessment

Data on illicit drug use in the last month and injecting behaviour were extracted from the patient’s substance use profile derived from EuroSUD, as part of intake and ongoing assessment.

Brief Addiction Recovery Status Scale (EuroSAAQ-BARSS) is a four-item scale developed by the researchers out of the EuroSAAQ. The four items come under two dimensions - ‘social adjustment status scale’ (SASS), which consists of two items,
current employment status and presence/absence of any pending court case, and the ‘general health status scale’ (GHSS) which consists of two items, appetite and sleep. The composite scores on those two dimensions go to form the BARSS score, which ranges between 4 and 8 (see Appendix). The BARSS demonstrates sufficient validity when correlated with Hunt et al’s Nottingham Health Profile (NHP).

EuroSUD and EuroSAAQ were translated from English into six European languages (French, German, Italian, Portuguese, Spanish, and Danish) and subjected to cross-validation to ensure comprehensibility and comparability of responses.

**Procedure**

Subjects were interviewed on-site during the course of their assessment for entry into the MST programme or, for patients already in treatment, as part of their routine follow-up appointments. Clinical researchers trained in the use of the instruments during the initial phase of the study conducted interviews. Interviews took an average of 40 minutes per subject. Urine samples were taken to verify drug use status both licit and illicit.

**Statistical analysis**

Stepwise multiple regression analyses were undertaken to evaluate the differences between IT groups and controls in the number of illicit drugs used and drug-abuse related QoL, with the effects of other predictors partialled out. One-sided t-tests evaluated the extent of differences. All categorical predictors enlisted in the regresional analyses were dummy-coded.

Logistic regression analyses were undertaken to evaluate the differences between IT patients and controls in the rates of illicit opiate use and injecting behaviour in the last month.

We estimated the effect size attributable to duration in treatment with drug abuse-related QoL. The following effect size formula was used: m1 - m2 /s, where m1 = mean score for each of the IT groups; m2 = mean score for controls; and s = pooled standard deviation of QoL scores. The rationale for calculating effect sizes was to identify a standard with which MST programmes’ effectiveness can be evaluated in future studies. All statistical analyses were undertaken using the SPSS for Windows.

**Results**

A total of 673 opiate-dependent patients attending 11 MST programmes in 8 European countries were recruited into the study. The majority (68%) of subjects were male, with a mean age of 32 years (SD = 5.9). Table 1 shows the sample characteristics.

Across centres, the percentage of males range between 49% (Paris, France) and 77% (Padua, Italy). The mean age range is between 29.8 (Dublin, Ireland) and 37.9 years (Arhus, Denmark). Table 2 shows the summary of sample characteristics by centre.

Multiple and logistic regression analyses were undertaken to test the first hypothesis, which stated that IT patients would report significantly lower numbers of illicit drugs used in the last month than controls. The separate IT groups reported significantly lower
The impact of methadone substitution therapy (MST) on illicit drug use and QoL was studied. Patients in the MST group (IT) reported significantly lower numbers of illicit drugs used in the last month than controls (IT1: t = -6.81, p < .00001; IT2: t = -7.61, p < .00001; IT3: t = -6.32, p < .00001; IT4: t = -10.14, p < .00001). These differences remained statistically significant even when centre effects were partialled out (Table 3). Furthermore, IT patients reported significantly lower rates of illicit opiate use than controls IT1 (OR = 0.04, 95%CI = 0.02, 0.08), IT2 (OR = 0.03, 95%CI = 0.08, 0.06), IT3 (OR = 0.04, 95%CI = 0.02, 0.08) and IT4 (OR = 0.02, 95%CI = 0.01, 0.04) (Table 3).

The second hypothesis, which stated that IT patients would report significantly lower rates of injecting than controls, was also confirmed IT1 (OR = 0.48, 95%CI = 0.24, 0.95), IT2 (OR = 0.21, 95%CI = 0.12, 0.37), IT3 (OR = 0.43, 95%CI = 0.22, 0.87) and IT4 (OR = 0.27, 95%CI = 0.13, 0.57). These differences were not affected by centre effects (Table 4).

The third hypothesis, which stated that IT patients would report a better drug-abuse related QoL than controls, was confirmed for patients who had been in treatment for at least 7 months (IT2: t = 4.43, p < .00001; IT3: t = 4.52, p < .00001; IT4: t = 6.22, p

### Table 1. Sample characteristics (n=673)

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean = 32; sd = 5.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (males)</td>
<td>68%</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>single</td>
<td>52%</td>
</tr>
<tr>
<td>married/coabiting</td>
<td>32%</td>
</tr>
<tr>
<td>separated/divorced/widowed</td>
<td>16%</td>
</tr>
<tr>
<td>Occupational status</td>
<td></td>
</tr>
<tr>
<td>unemployed</td>
<td>54%</td>
</tr>
<tr>
<td>employed</td>
<td>39%</td>
</tr>
<tr>
<td>student/retired</td>
<td>7%</td>
</tr>
<tr>
<td>Accommodation</td>
<td></td>
</tr>
<tr>
<td>parental home</td>
<td>30%</td>
</tr>
<tr>
<td>owner occupied</td>
<td>8%</td>
</tr>
<tr>
<td>rented</td>
<td>54%</td>
</tr>
<tr>
<td>NFA/Hostel</td>
<td>8%</td>
</tr>
<tr>
<td>Lifetime history of injecting</td>
<td>92%</td>
</tr>
<tr>
<td>Lifetime sharing</td>
<td>70%</td>
</tr>
</tbody>
</table>
Table 2. Sample characteristics by centre

<table>
<thead>
<tr>
<th>Centre</th>
<th>Sample size</th>
<th>Mean Age (SD)</th>
<th>Sex: male (%)</th>
<th>Lifetime history of injecting (%)</th>
<th>Lifetime history of sharing (%)</th>
<th>Employed (%)</th>
<th>Single (%)</th>
<th>Unstable residence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dublin</td>
<td>60</td>
<td>29.8 (5.3)</td>
<td>68</td>
<td>90</td>
<td>78</td>
<td>7</td>
<td>59</td>
<td>3</td>
</tr>
<tr>
<td>Oporto</td>
<td>100</td>
<td>31.6 (5.4)</td>
<td>73</td>
<td>87</td>
<td>72</td>
<td>63</td>
<td>47</td>
<td>10</td>
</tr>
<tr>
<td>Essen</td>
<td>82</td>
<td>30.3 (5.6)</td>
<td>66</td>
<td>98</td>
<td>78</td>
<td>24</td>
<td>63</td>
<td>6</td>
</tr>
<tr>
<td>London</td>
<td>99</td>
<td>33.9 (7.2)</td>
<td>67</td>
<td>85</td>
<td>61</td>
<td>31</td>
<td>42</td>
<td>6</td>
</tr>
<tr>
<td>Bergamo</td>
<td>76</td>
<td>31.0 (4.8)</td>
<td>72</td>
<td>100</td>
<td>71</td>
<td>49</td>
<td>73</td>
<td>17</td>
</tr>
<tr>
<td>Padua</td>
<td>52</td>
<td>31.5 (5.2)</td>
<td>77</td>
<td>80</td>
<td>39</td>
<td>50</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>Ringkobing</td>
<td>27</td>
<td>35.9 (4.9)</td>
<td>74</td>
<td>96</td>
<td>70</td>
<td>50</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>Oviedo</td>
<td>35</td>
<td>30.7 (4.4)</td>
<td>74</td>
<td>91</td>
<td>69</td>
<td>34</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>Paris</td>
<td>47</td>
<td>34.5 (6.7)</td>
<td>49</td>
<td>95</td>
<td>68</td>
<td>30</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>Arhus</td>
<td>35</td>
<td>37.9 (4.7)</td>
<td>77</td>
<td>97</td>
<td>94</td>
<td>74</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Barcelona</td>
<td>60</td>
<td>31.0 (5.7)</td>
<td>60</td>
<td>97</td>
<td>78</td>
<td>24</td>
<td>41</td>
<td>8</td>
</tr>
</tbody>
</table>
Furthermore, there was a consistently positive relationship between duration in treatment and QoL scores (Figure 1).

Effect size between controls and IT Groups ranged between moderate and high for drug-abuse related QoL (Table 5).

**Discussion**

This is a cross-sectional study of two groups of patients - those new to treatment and those in treatment for 2 or more months. The significant differences we observed in these two groups can only be regarded as a measure of the impact of MST on illicit drug use and drug abuse-related QoL. Little can be inferred from this study about the effectiveness of MST, which could only be evaluated in a longitudinal study on a cohort of newly admitted patients. Furthermore, although at a macro level the MST programmes in the study were similar, it is possible that individual programme attributes may have confounded the results in some way, even though centre effects were partialled out in

Table 3. Differences in the number of illicit drugs used in the last month and rate of illicit opiate use in last month between different IT groups and controls

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Number of illicit drugs used in the last month</th>
<th>Illicit opiate use in last month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized beta</td>
<td>t</td>
</tr>
<tr>
<td>IT1 (2-6 mths)</td>
<td>-0.25</td>
<td>-6.81</td>
</tr>
<tr>
<td>vs controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT2 (7-18 mths)</td>
<td>-0.28</td>
<td>-7.61</td>
</tr>
<tr>
<td>vs controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT3 (19-36 mths)</td>
<td>-0.23</td>
<td>-6.32</td>
</tr>
<tr>
<td>vs controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT4 (&gt;37 mths)</td>
<td>-0.37</td>
<td>-10.14</td>
</tr>
<tr>
<td>vs controls</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The following predictors with significant influence on either number of illicit drugs used in the last month or QoL were controlled for marital status and education.
In spite of these limitations, our findings are consistent with those from previous reports of the impact of MST on problematic drug use. In any case, our findings relating to the influence of MST on drug-abuse related QoL have not been previously reported.

The following predictors with significant influence on either injecting or use of illicit opiate use were controlled for centre, accommodation, marital status and education.

### Table 4. Differences in rate of injection of illicit drugs in last month and drug abuse-related QoL

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Injecting in last month</th>
<th>Drug abuse-related Quality of Life (QoL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>IT1 (2-6 mths) vs controls</td>
<td>0.48</td>
<td>0.24, 0.95</td>
</tr>
<tr>
<td>IT2 (7-18 mths) vs controls</td>
<td>0.21</td>
<td>0.12, 0.37</td>
</tr>
<tr>
<td>IT3 (19-36 mths) vs controls</td>
<td>0.43</td>
<td>0.22, 0.87</td>
</tr>
<tr>
<td>IT4 (&gt;37 mths) vs controls</td>
<td>0.27</td>
<td>0.13, 0.57</td>
</tr>
</tbody>
</table>

Note: The following predictors with significant influence on either injecting or use of illicit opiate use were controlled for centre, accommodation, marital status and education.

### Table 5. Effect sizes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Drug-related QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls vs IT1</td>
<td>ns</td>
</tr>
<tr>
<td>Controls vs IT2</td>
<td>0.58</td>
</tr>
<tr>
<td>Controls vs IT3</td>
<td>0.66</td>
</tr>
<tr>
<td>Controls vs IT4</td>
<td>0.80</td>
</tr>
</tbody>
</table>
In-treatment (IT) patients, who were classified according to duration in treatment, performed better than controls on all impact criteria, except for the IT1 (patients 2-6 months in treatment) whose QoL did not differ from that of controls. This observation may suggest that the threshold for drug abuse-related QoL occurs later than 6 months following admission into treatment. Furthermore, related to QoL, the items on the social adjustment scale of BARSS (i.e. employment status and the presence/absence of any pending court case) are generally unlikely to be affected within the early period of treatment.

The study findings have, therefore, demonstrated the ability of MST to impact positively on illicit drug use, patients’ overall functionality, and on public health, through lower risks of injecting in IT patients. Moreover, the findings of this transnational study demonstrate that MST is a culture-free and ecologically valid treatment modality for opiate dependence. This novel observation is evident in the fact that IT patients performed better than controls on impact criteria, even when centre effects were partialled out in the analyses.

We have also been able to identify treatment effect sizes that can provide benchmarks for future studies on the effectiveness of MST.
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Acknowledgements

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1. Dole VP, Nyswander N. A medical treatment for diacetylmorphine (heroin) addiction. JAMA, 1965: 193, 80-84

APPENDIX. Brief Addiction Recovery Status Scale [BARSS]

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Please consider your situation in the last month)</td>
<td></td>
</tr>
<tr>
<td>1. Are you currently employed?</td>
<td>Yes=2  No=1</td>
</tr>
<tr>
<td>2. Do you at present have any court cases pending?</td>
<td>Yes=1  No=2</td>
</tr>
<tr>
<td>3. What is your appetite like?</td>
<td>Good=2  Poor=1</td>
</tr>
<tr>
<td>4. How do you sleep?</td>
<td>Well=2  Poorly=1</td>
</tr>
</tbody>
</table>

Acknowledgements

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When “enough” is still not “enough”.

Effectiveness of high-dose methadone in the treatment of heroin addiction

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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
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. 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.

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. 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.

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 [15].

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 [26].

**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 [45]. 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 [17-20].

**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 [3].

**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)[6].

**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) [16].

**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 [4].

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 [5].

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 [22].

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 [21].

Handal and Lander, 1976

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

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.

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).

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 [25].

**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 [49].

**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) [8].

**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 [37].

**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 [44].

**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 [24].

**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,
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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 [2].

**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 [1; 28].

**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 [7].

**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 [9].

**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 [51].

**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 [39].

Maxwell & Shinderman, 1999

High methadone dosages improve patients’ outcome [42]. Maxwell & Shinderman from the “Centre for Addictive Problems” in Chicago enrolled 164 incompliant 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 incompliant 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 [50].

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 [36].

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±84 mg/day, whereas an average 99±49 mg/day was required for uncomplicated peers. Over a 990-day period no differences were found in treatment retention.\(^{[40]}\)

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 ≥ 12 weeks for 28%)\(^{[27]}\).

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\(^{[48; 54]}\). 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\(^{[10; 13; 14]}\) 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\(^{[38]}\) 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\(^{[4; 22; 26; 37]}\) failed to discover any evidence against these findings by Ling and colleagues\(^{[38]}\).

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\(^{[19; 20]}\) & Stitzer and colleagues\(^{[49]}\) also suggested that a rapid, sharp increase in dosages may
produce a decisive impulse towards abstinence from opiate us, 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 [40], with an official maximum of 780 mg/day [42]. 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 [16] provided the most accurate results, showing no real advantage in prescribing 50 mg rather than 30 mg. Other studies [17-20] did not reach clear-cut conclusions. Berry’s work [3] 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 [53]). In reviewing the factors that have been shown to influence the pharmacological effectiveness of methadone, Kreek [31; 34] 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 [52], 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 [41]. The same authors reported that the compliance with treatment of psychiatringly ill heroin addicts improved significantly when high dosages were used [40].
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[11]”. 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 [35].

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.

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The impact of continuing terror and stress on the use of psychoactive drugs in Israel

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Summary

An unprecedented wave of terrorism has plagued the Israeli population over the last two years. Between September 29, 2000 and October 1, 2002, Magen David Adom recorded a total of 4,535 casualties. Of these, 539 people were killed, 406 severely injured and 554 moderately injured. Among the additional 3,036 people lightly injured were 11 MDA staff members. Fears of random shootings and of human bombs exploding in schools, restaurants, and buses have caused extreme stress in the general population. Because the country is so small, everyone knows a terror victim personally – or knows someone else who does. At the same time, the economic situation, with its rising unemployment, reflects both the reality of war and the international recession. Stress and uncertainty are widespread.

This ongoing study explores the assumption that terror, stress and uncertainty influences the prescribing practices of community physicians. Initially, we were interested only in psychoactive drugs, namely anxiolytics, hypnotics and antidepressants. However, as this pilot study was planned to become part of a larger study done by the Mental Health Services, we then decided to include analgesics, asthma medications and H1 antagonists for hyperacidity and anti-hypertensives. We believed that by measuring changes in prescribing patterns and actually measuring the dispensing of these medications, we would also receive a certain picture regarding the coping mechanisms of Israeli society. This is retrospective study, utilizing prescribing and dispensing data from some of the major HMOs’ computerized data bank. The data were to be evaluated in terms of DDD/1000 population for given categories of medication. Our study, like the situation in Israel, is ongoing. Even as this article is being written (in late December 2002), the Israeli medical establishment, along with the rest of the country, is preparing for the possibility of Iraqi chemical and biological warfare. As can be imagined, the fluidity of our security situation has affected the planned study many times over, and forced us to reconsider our goals, scope, and methodology. Indeed, our initial study has since been incorporated into a larger, national study under the

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Heroin Addiction and Related Clinical Problems

Introduction

An unprecedented wave of terrorism has plagued the Israeli population over the last two years. Between September 29, 2000 and October 1, 2002, Magen David Adom recorded a total of 4,535 casualties. Of these, 539 people were killed, 406 severely injured and 554 moderately injured. Among the additional 3,036 people lightly injured were 11 MDA staff members. Fears of random shootings and of human bombs exploding in schools, restaurants, and buses have caused extreme stress in the general population.

"Each morning when I leave my apartment building, I have an important question to contemplate: Should I turn left or should I turn right? This question may seem inconsequential, but the events of the past few months in Israel have led me to believe that each small decision I make – by which route to walk to school, whether to go out to dinner – may have life-threatening consequences."

Marla Bennett wrote these lines some 4 months before she was killed by a terrorist bomb in a cafeteria at the Hebrew University in Jerusalem. Israel 2002 is not a normal society. Israel, in the light of her continued terrorist attacks, has become a “laboratory” for testing the coping mechanisms of a society under stress.

Professor Avi Blich, director of the Lev HaSharon Psychiatric Hospital, has examined the coping mechanisms of the Israeli population under trauma. He found that approximately 10% of the population suffers from symptoms of PTSD, the majority of them women. Dr. Yacov Polokovitz, director of the Department of Internal Services for Mental Health in the Israeli Ministry of Health, states that after every terrorist incident, there are far more injured people than meet the eye. For each person physically injured in an attack, he explains, there are between ten and twenty others, often relatives and bystanders, who remain severely traumatized and anxious. A full 40% of these patients are minors.

Dr. Galil Wistov, director of the Children and Youth Psychiatric Department at Hadassah Hospital, observed young people in Jerusalem during July 2002, a period of particularly intense terrorist activity in that city. He too concluded that 40% of these young...
people exposed to terrorist events continue to suffer from symptoms of PTSD\textsuperscript{4}.

Yet, the question of whether specific segments of our population are suffering from PTSD or acute trauma is actually irrelevant to this study. This is because our entire society has been living under extreme stress over an extended period of time. How do we cope?

**Objectives**

This ongoing study assumes that terror, stress and uncertainty influence the prescribing practices of community physicians. We also expect to explore the behaviour of the medical staff in primary health clinics, and to learn if patients actually fill their prescriptions. Initially, we were interested only in psychoactive drugs, in anxiolytics, hypnotics and antidepressants. This seemed like a normal follow up to Yagur-Green-spoon-Ponizovsky’s study of the “Primary Care Clinic Attenders Under War Stress”\textsuperscript{5}. In that study of the residents of Gilo, a Jerusalem neighbourhood exposed to frequent gunfire, it was assumed that emotional distress would correlate with actual periods of attack. It was assumed, also, that this distress would be reflected in frequent prescriptions of psychotropic medication. Drugs were not categorized, however; the use of specific drugs was not included in the database.

When our pilot study recently became part of a larger study initiated by the Mental Health Services, we re-evaluated and expanded our initial objectives. We decided to address a larger population than first envisioned. We also expanded it to include a wider list of drug use than originally planned. (I must note here that the Ministry also plans to study the public’s use of tobacco and alcohol as coping mechanisms in the face of prolonged stress—but in another framework entirely.)

In our study, we plan:

- to monitor the number of patient visits to their primary care provider over a specific period of time;
- to itemize and classify the amount and types of prescriptions issued by the doctors;
- to contrast our findings with actual dispensing by the pharmacist;
- to compare drug utilization in different types of populations and geographic areas;
- to utilize computerized databases provided by the Israeli HMOs to evaluate prescribing patterns of physicians based upon gender, age and perhaps by their year of immigration;
- to enlarge the database of the drugs to be evaluated – to include the analgesics, anti-hypertensives and drugs used to treat autoimmune diseases such as asthma and psoriasis.

We assumed that easy access to medical care and prescription drugs through the nationalized HMOs would be translated into statistically large increases in all types of psychoactive drugs, analgesics, and particularly, asthma medications, under the
influence of ongoing violence and stress. These findings were corroborated in “Self-Reported Increase in Asthma Severity After the September 11 Attacks on the World Trade Center.”

We also assumed that the drug use of certain populations - the ultra-orthodox, national religious, and settlers for example, would contrast with populations such as new immigrants who had not yet acclimated to our way of life. According to the literature, members of communities offering religious or ideological support tend to cope more easily with stress and trauma. This would likely affect the number of visits by patients to clinics, and the prescription drugs dispensed.

Methods

This is a retrospective study, based on prescribing and dispensing data gathered from the computerized data banks of most of the major HMOs of Israel. These data, which cover both national and regional levels, were to be evaluated in terms of DDD/1000 population for given categories of medications as defined by ATC classification. Regions of high incidence of terrorist attacks were to be contrasted with those of low incidence. The study was to utilize pre-Intifada drug data as a baseline.

As stated previously, both the prescribing behaviour of physicians and actual pharmacy dispensing would be analysed, while taking into account the socioeconomic and cultural differences within the population. Our fellow colleagues suggested that we concentrate solely on Jerusalem as the active laboratory, since it would be relatively simple to stratify and classify the different neighbourhoods and populations according to our study needs. In this way, we would also compliment the Gilo study.

In addition, we were influenced by Professor Avi Blich’s study on national PTSD that included data on a large percentage of females. We too considered it essential to analyse the dispensed prescription data according to gender and age (16-65).

Results

This study, like the situation in Israel, is ongoing. Even as this article is being written (in late December 2002), the Israeli medical establishment, along with the rest of the country, is preparing for the possibility of Iraqi chemical and biological warfare. The fluidity of our security situation has affected the goals, scope and methodology of our project. As stated earlier, our initial study has been incorporated into a national study by the Mental Health Services of the Ministry of Health under the auspices of Dr. Greenspoon. While we will continue to investigate the prescribing and dispensing patterns of psychoactive drugs, the other goals mentioned earlier will also be assessed.

At this date, only initial dispensing data has been analyzed, but if what we see holds true, our findings are of great significance. Initially we assumed that there would be an increased use of anxiolytics and hypnotics, either of benzodiazepine derivatives and benzodiazepine-related drugs. Instead, we found no statistical increases in either.
The use of antidepressants proved most interesting: we noted a significant increase in SSRI dispensing, and to our surprise, it was not at the expense of traditional antidepressants.

It must be emphasized that our findings are preliminary, raw data.

It is difficult to discuss the implications of this study with only partial data. However, if our preliminary findings follow through, we see a change in prescribing habits by primary care providers. We see benzodiazepines substituted by SSRIs, on account of their anxiolytic effect. If this is the case, we must study and analyze the long term use of SSRIs, including their usage by the “non-typical” depressed population.

We are anxiously awaiting the arrival of additional data from other sources, data that study a wider variety of drugs than originally planned. Through our efforts, we hope to attain a clear picture of the prescribing patterns of Israeli physicians and the coping mechanisms of Israel, a society living under prolonged stress.

Discussion

Israel is indeed a psychological and sociological laboratory for the study of coping under prolonged stress. But are there universal lessons to be learned from our unique experience?

Several years ago, I had the privilege of discussing just this question with Dr. Andrea Barthwell.

This was before September 11 and before the Intifada with its human bombs. It was Andrea who said that for Americans, it was perhaps the urban inner city battlegrounds with their gang violence and drive-by shootings that could best be compared with the Israeli experience. In conclusion, when this study is completed, we envision communities that develop support systems designed to strengthen their members’ coping abilities. We envision primary care medical providers trained to ease the suffering of those populations plagued by 21st century surrealistic violence.

References

Reduction in self-reported nicotine dependence after stabilization in methadone maintenance treatment

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Summary

ICD-10 criteria have been used for the assessment of opioid dependence and the Fagerstrom Tolerance Questionnaire (FTQ) to assess tobacco smoking. The mean methadone dose was 106 mg (SD=45) in the studied group, after twelve months in the methadone maintenance treatment programme (MMTP). The mean FTQ score was 6.5 (SD+1.8) before entering, 5.6 (SD+2.1) after stabilization in the MMTP (p<0.001) and 3 were non-smokers at the time of the second FTQ testing. No smoking cessation programme has been implemented. The findings do show a tendency for nicotine dependence among patients to fall in their period of stabilization in the MMTP.

Key words: nicotine dependence - methadone maintenance - methadone dose - methadone plasma concentration - opioid

Introduction

Tobacco dependence is common among users of other drugs, with tobacco smoking prevalence ranging between 85% and 100% in abusers of alcohol, opioids and cocaine [¹,²,³]. Among the five categories of primary drugs abused surveyed, heroin users had the highest level of smoking in Stark’s study [⁴]. Tobacco-related diseases are a leading cause of death in patients previously treated for alcohol dependence and/or for other non-nicotine psychoactive substance dependencies [⁵,⁶]. Chiat [⁷] and Schmitz [⁸] reported
that the administration of methadone results in substantial, dose-related changes in rates of cigarette smoking by methadone-maintained patients. High rates of smoking among methadone maintenance patients were also described by Clemmey \[9\]. However, Frosch et al.\[10\] demonstrated in their study that illicit substance use, as measured through urine toxicology, was found to increase in a stepwise fashion from non-smokers, to chippers, to heavy smokers. Methadone patients who smoke more are significantly more likely to report problems of not feeling “held” by their methadone dose \[11\].

The use of nicotine in association with opioid use can pose the question whether this is directed towards a search for rewarding effects through pharmacological brain stimulation, or whether it is an attempt at self-medication of withdrawal symptoms. The objective of the study was to find out if, in the context of the Methadone Maintenance Treatment Programme (MMTP), without any rigid general prescription scheme, or firm ceiling for dosage, and where (1) no signs of withdrawal, (2) no craving and (3) no illicit opiate use are the three guiding principles and indicators of proper dose assessment \[12,13\], there is any change in smoking habits after stabilization of the patients in the programme. The hypothesis was that there would be no increase in nicotine dependence among patients in the MMTP after their stabilization.

**Patients and Method**

The MMTP in Bratislava (Slovak Republic), from which the study sample was chosen, had an overall retention rate of 84% after 12 months. There was a proportion of 13% of urine samples which tested positive for morphine. These outcome indicators were presented in The Report on Methadone Maintenance Treatment, which was submitted by The Centre for Treatment of Drug Dependencies to The Slovak Ministry of Health in 2001. Apart from a diagnosis of opioid dependence, additional inclusion criteria were required for admission to the MMTP: age 18 years and over, and at least two documented unsuccessful attempts at medical detoxification with no sustained abstinence. The programme, which was complex, consisted of medical and psychiatric services, group therapy, a cognitive-behavioural approach and contingency management. Methadonium chloratum was dispensed in liquid form mixed with juice at the methadone outpatient clinic. Take-homes were allowed for weekends. At a later stage, patients were allowed to collect methadone twice a week, with the preconditions that they had not had any positive urine tested for morphine in the past twelve months and the daily dose should not exceed 200 mg.

The studied group consisted of 138 subjects who were admitted to the MMTP in Bratislava. The second FTQ testing was conducted during regular status examination after one year of treatment. There were 76% males and 24% of females in this group. The average age was 27.3 years (SD+5.0) in a range between 19 and 44 at the time of their entry to the programme. There were 137 (99%) tobacco smokers and 1 (1%) non-smoker in the group at the time of intake to the programme.

The study had a prospective, clinical design. ICD-10 \[14\] diagnostic criteria were used
to assess the diagnosis of opioid dependence. The Fagerstrom Tolerance Questionnaire (FTQ), in its 8-item version [15], was used to measure nicotine dependence. The FTQ was administered for the first time during the pre-entry interview at the time of intake into the MMTP and after one year of treatment. The survey was conducted from June 2001 to June 2002. The correlation between the FTQ score and daily methadone dose was studied in the whole group, and correlation with the methadone concentration in plasma was studied in the subgroup of 64 patients from the sample. Their blood was taken for plasma level assessment after 12 months of being in the programme and the FTQ was administered simultaneously. Quantitative analysis of blood samples for methadone was performed in an analytical laboratory, where the GC/MS methodology was used. Using SPSS statistical software, the following methods were applied: t-test for two independent samples, t-test for matched pairs, one-way ANOVA, Kolmogorov-Smirnov test for goodness of fit, Pearson correlation coefficient.

Results

The average dose of methadone was 106 mg (SD=45; median 100 mg, in the range between 10 and 230 mg). The frequency distribution curve for doses in the studied group was approximately bell-shaped (Fig. 1). It was tested by a Kolmogorov-Smirnov test. The mean daily dose of methadone in the subgroup of 64 patients, where methadone plasma concentrations were assessed, too, was 107 mg (SD=40; median 100 mg, in the range between 30 and 190 mg).

There were 3 non-smokers at the time of the second FTQ testing: 1 (0.7%) preserved

Figure 1. Frequency distribution of daily methadone doses in the group
his non-smoking status, which he had prior to the MMTP and 2 (1.4%) gave up smoking while they were in the programme. The mean FTQ score for nicotine dependence was 6.5 (SD=1.8) prior to entering methadone maintenance vs. 5.6 (SD=2.1) at the time of stabilization. The difference between these two mean scores was statistically significant (p<0.001; 95%, CI 0.6-1.2). Graphic illustration is provided by two line-charts of score distributions (Fig. 2). No statistically significant differences were confirmed between genders in relation to dosages and FTQ scores. Test-retest reliability of the FTQ was measured (Pearson r=0.535; p<0.01).

No significant correlation was found between the daily methadone dose and the FTQ score, or in the whole studied group (Pearson r=0.090; NS). In the subgroup where plasma concentrations were measured, the correlation between admission FTQ and the dose after one year of treatment was significant at the 0.05 level (Pearson r=0.252; p=0.047); but the correlation disappeared after a year (Pearson r=0.159; NS). No correlation was found between the level of methadone in the plasma and the FTQ score in this subgroup (Pearson r=-0.033; NS).

**Discussion**

The frequency distribution curve for daily methadone doses was approximately bell-shaped in the studied group. Still, there was a tendency towards a slight shift to the right. This was probably due to the fact that daily doses of methadone above 200 mg were not allowed by the programme for the twice-a-week take-homes; this restriction
was indirectly pushing some of the patients to reduce their daily dose demands below this limit.

We detected a very high proportion (99%) of tobacco smokers among patients with opioid dependence in this sample at the time of their entry to the MMTP. Despite the fact that nicotine has been and continues to be the most common substance abused by patients with opioid dependence, very little is known about optimum treatments for the reduction and cessation of tobacco use in these dual diagnosis patients. There are, however, studies that indicate the feasibility of treating cigarette smoking in the context of drug dependence therapy, especially within the framework of opioid dependence treatment [6,9,16].

According to Nestler [17], endogenous opioid pathways have been implicated in the acute reinforcing effects, not only of opiates, but also of other abused drugs, particularly alcohol and nicotine. Preliminary pharmacological evidence suggests that there is an opioid component in nicotine dependence. Nicotine-dependent subjects showed naloxone dose-dependent increases in withdrawal signs and craving [18]. On the other hand naltrexone was found to significantly reduce craving and the total number of cigarettes smoked in nicotine-dependent subjects [19].

The psychometric characteristics of the Fagerstrom Tolerance Questionnaire and its versions, as an instrument for measuring nicotine dependence, have been discussed in several studies resulting in the conclusion that it is useful [14, 20, 3, 21]. Our principal hypothesis, based on our clinical impressions, has been confirmed by the findings of this study, which detected not only that there was no increase in nicotine dependence, but that there was actually a decrease in the mean FTQ score among patients after their stabilization in the MMTP (from 6.5 to 5.6). It is interesting that the FTQ score was found to be much higher among patients on methadone maintenance in the work of other authors, e.g. 7.5 in Clemmey’s [9] study. High rates of smoking among methadone patients, which have been attributed to their desire to intensify the effect of opiates [1], seem to have been a less prevalent cause in this group. Despite finding an increase in smoking after an increase in methadone doses, Stark & Campbell [22] found that maintenance doses were not correlated with smoking levels. This might suggest that the acute effects of methadone on smoking are nullified as clients get used to the dose level. This is also consistent with our results. What is important to mention is that no correlation between the methadone dose and the FTQ score (intensity of dependence) was found, but also no correlation could be demonstrated between the FTQ and the concentration of methadone in plasma. This is interesting in association with the unclear influence of smoking on methadone plasma levels. Prevailing opinion, according to Eap [23], was that smoke increases methadone plasma clearance and so induces its faster elimination from the body. However, in an in vitro study, human liver microzomes, CYP1A2, did not seem to be involved in the methadone metabolism.

Stabilization on individually tailored doses of methadone, which was associated with a large decrease in the occurrence of opioid withdrawal signs, and in craving, and with a decrease in the use of illicit opiates, could be the basis for this significant change in
smoking habits among the methadone patients in our group. The approach which excludes upper methadone dose limits exists can provide that opportunity. The hypothesis can be put forward that if there is a higher proportion of patients in any MMTP who are on lower methadone maintenance doses and are simultaneously taking illicit opiates, that they are not fully stabilized, so the cigarettes are used as self-medication for the signs of discomfort. This would be consistent with Frosch’s [10] findings.

It seems that high rates of cigarette smoking are not an inevitable future for patients in MMTPs. On the basis of these findings, it might be presumed that comprehensive methadone maintenance treatment programmes themselves, with appropriate, individually assessed dosing, could be associated with a reduction in the intensity of nicotine dependence and might be a good starting point for the application of targeted tobacco cessation programmes among patients treated for opioid dependence.

These findings would need further replications in different MMTPs. Also, other objective methods for the assessment of tobacco smoking, such as the measurement of carbon monoxide levels in used air and that of plasma cotinine levels should be applied in studies with a similar design in the future.

Conclusions

Based on the results of this study, it seems that a high level of tobacco dependence is not an inevitable future for patients in MMTPs. We presume that methadone maintenance treatment itself, with appropriate, individually assessed dosing can contribute to the reduction of nicotine dependence and that is a precondition for further effective tobacco cessation efforts among patients treated for opioid dependence.

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References


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Liver cytochrome overexpression in human HCV infection

Ernesto De Bernardis & Lina Busà

Sir,

The manuscript by S. Maxwell et al., “Correlation between hepatitis C serostatus and methadone dose requirement in 1,163 methadone-maintained patients”, published in Heroin Add & Rel Clin Probl 2002, 4(2): 5-10, suggests the need for higher maintenance doses of methadone in HCV-infected patients. It is stated in the discussion that “whereas most other hepatitides impair the activity of the Cytochrome P450 enzyme system, our clinical observations are more consistent with a cytochrome induction phenomenon. This possibility deserves further study, as it could have significant impact on the treatment of HCV and related conditions”.

Indeed, a correlation between viral hepatitis and the induction of selected isozymes of the cytochrome P450 family was published in 1996 by G.M. Kirby and coworkers (6). The Authors report that in HCV-infected human liver, CYP2A6, CYP3A4 and CYP2B1 were overexpressed in hepatocytes with hemosiderin pigmentation.

It is known that the main catabolic pathway for methadone depends on CYP3A4, with minor contributions from other isozymes (3,4).

Hence, the overexpression of CYP3A4 may be at least partly, responsible for the higher methadone doses reported by Maxwell and coworkers for HCV-infected opioid-dependent subjects. Since cannabinoids and diazepam are known to inhibit CYP3A4, a pharmacokinetic interference determining lower clearance of methadone and less crabbing and discomfort could contribute to their use by these patient populations.

Interestingly, buprenorphine is also metabolized by CYP3A4 (5); this calls for an evaluation of required dosages in HCV-infected vs. seronegative individuals.

Other mechanisms might also influence the bioavailability of opiate drugs in viral hepatitis. P-glycoprotein (PGP), a membrane transporter which extracts various cationic xenobiotics, including methadone, from cytoplasm could be a candidate. To our knowl-
edge, no published studies have reported clinically significant effects on methadone pharmacokinetics by PGP inhibition, but the Italian drug package insert for methadone hydrochloride states that PGP inhibitors may increase methadone blood levels\(^1\). Some in vitro investigations suggest that HBV infection with integration of the virus into hepatocyte DNA may induce the synthesis of PGP\(^2\). To date, no reports are available on the effects of HCV infection on the hepatic expression of that transporter. The direction and magnitude of those effects on PGP function, and their possible clinical relevance, could be an interesting additional route open to investigation.

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INFORMATION FOR CONTRIBUTORS

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