

Psychiatric Severity and Treatment Response in Methadone Maintenance Treatment Programmes: New Evidence

**Pier Paolo Pani, Emanuela Trogu, Gianfranco Carboni,
Patrizia Palla and Anna Loi**

Summary

Recent studies have shown that the presence and severity of psychiatric comorbidity in opioid addicts enrolled in methadone maintenance programmes does not interfere with the outcome of treatment evaluated in terms of retention in treatment and heroin use. On this basis we started a cohort prospective study, in order to gather information on the impact of psychiatric severity on different outcome indicators of the treatment (retention, craving, use of heroin and cocaine, psychiatric status). The results obtained from the first 78 patients enrolled in the study show no significant differences, in terms of retention in treatment or of heroin and cocaine use, between patients with high (44% of the cohort) and low (56% of the cohort) psychiatric severity. Regarding psychiatric status, almost all the psychopathological dimensions explored by SCL-90 show a significant reduction in symptoms during the course of the treatment, with a significantly higher improvement in patients with a severe psychopathology. Methadone dose tended to be higher in patients with high psychiatric severity. Moreover these patients had a significantly greater involvement in psychopharmacological treatments. The results of this study are consistent with those of previous ones showing that the severity of psychiatric comorbidity does not substantially alter the efficacy of maintenance methadone treatment

Key words: Methadone maintenance - Psychiatric comorbidity
- Psychopathology - Addiction - Dual Diagnosis - Heroin

Introduction

Few of the studies that have investigated the influence of psychopathology on the

Address for reprints: Pier Paolo Pani, MD. - SerT AUSL 8, Via dei Valenzani, 09131 - Cagliari, Italy, EU

results of treatment for opioid addiction have been specifically designed for patients in methadone maintenance treatment. Methadone-maintained patients have, in fact, often made up only a small proportion of the total population considered.

Taken as a whole, these studies have suggested a worse outcome for the treatment of patients suffering from an additional psychiatric disorder^{15,17,18,19,20,26}. However, the indicators chosen to evaluate treatment results did not necessarily include the variables most closely linked with the effects of methadone, such as retention in treatment. Moreover, the evaluation of the effects of psychopathology on toxicological results has yielded controversial results^{24,25,14,26}.

Several variables have been used to quantify the outcome of treatment in a variety of areas (such as health, work and legal problems), but retention in treatment and toxicological urine results have continued to play a leading role in evaluating the efficacy of pharmacological treatments for opioid addiction²⁷.

Some years ago, we conducted a study to verify the impact of psychiatric comorbidity on the results of treatment in a comprehensive methadone maintenance treatment programme (MMTP) which included psychiatric care²². In this study, patients referred by their physician to a psychiatrist for consultation were compared with those not needing any consultation. The variables used to verify the results of the treatment were retention in treatment and positive urinary tests for opioids. Methadone doses were also compared, as a potential confounding factor.

The results of the study showed that patients with an ascertained additional psychiatric disorder performed as well as the others both in terms of heroin use and retention in treatment. However, patients who had a more severe psychopathology received a greater number of interventions. Moreover, during the two years of observation, patients with a known psychiatric comorbidity tended, on average, to take a higher methadone dose than those with no known psychiatric comorbidity, even if this difference did not reach statistical significance.

More recently, a study carried out by Maremmani et al.,¹⁶ on a cohort of heroin addicts enrolled in an MMTP, showed that opioid addicts with an additional psychiatric diagnosis (DSM-IV axis I) had a retention rate in treatment significantly higher than that of other patients. Moreover, the average methadone dose taken by these patients was significantly higher (154 mg versus 99 mg) than that taken by patients with no additional Axis I diagnosis.

A later study, by Cacciola et al.³ evaluated the relationship between the presence of psychiatric comorbidity and the results of treatment in opioid addicts recently admitted to an MMTP. After seven months, participants in the study showed a decrease in the use of substances, as verified by toxicological urinary analyses. No differences were attributable to the presence of psychiatric comorbidity. In this study too, other areas related to substance abuse - the legal, family/social and psychic ones - were investigated. The improvement of the status of patients was confirmed in these areas, independently of the presence of additional psychopathology. In this study too, patients with additional psychopathology received a significantly higher number of psychiatric

interventions. Unfortunately, the differences between methadone doses among groups were not investigated, so excluding any evaluation of the role methadone may have played in determining the results.

These studies, carried out within the context of comprehensive methadone maintenance programmes, were consistent in showing the positive effects of treatment on patients with psychiatric comorbidity, both in terms of heroin use and retention in treatment. A substantial improvement in specific indicators of psychiatric severity for patients has also been shown³. The positive outcomes observed seems to be directly correlated with the intensity of the treatment^{22,3} and with the mean methadone dose taken^{22,16}.

The general validity of the results of these studies is limited in some ways: the Pani et al. study was a retrospective one, so it did not include any extensive analysis of factors potentially confounding the relationship between psychopathology and treatment results; also, the Pani et al. and Maremmanni et al. studies did not investigate the outcome of treatment on specific psychiatric variables; the Cacciola et. al. study³ did not consider the potential influence of methadone dosages on treatment results.

As these studies gave a positive indication on the outcome of patients with psychiatric comorbidity, despite the limitations just mentioned, we started a prospective investigation of the impact of psychopathology on the outcome of treatment for opioid addicts admitted to a methadone maintenance treatment programme.

This study, a cohort prospective study, was designed to gather information on the impact of psychiatric severity on a number of treatment outcome indicators (retention, craving, use of heroin and cocaine, psychiatric status). It also included the assessment of potential confounding factors pertinent to patients (socio-demographic or clinical) or to treatment (intensity and quality of care, methadone dosages). Moreover, as the predictors of the early and later treatment results are not necessarily the same, the outcome evaluation was extended to two years.

The study started in May 2000 and around 150 patients have been enrolled so far.

The present paper reports the results recorded for the cohort enrolled in the first year.

Materials and methods

Setting

The study was carried out at the Via dei Valenzani Drug Addiction Service (Servizio Tossicodipendenze, or SER.T.) run by health district No. 8 (Azienda Unita' Sanitaria Locale, AUSL8) in Cagliari, Italy. This service offers various different types of treatment for addictive disorders and related problems (detoxification, methadone-, buprenorphine-, and naltrexone-maintenance, general medical care, counselling, rehabilitation services, and psychological-psychiatric care).

In this low-threshold programme, clinical staff provide easy access to treatment and then aim to prolong the retention of patients in the programme. In order to supersede the

risky life-style associated with heroin addiction, methadone dosing usually starts soon after the patient receives a diagnosis of opioid dependence (with physical dependence). Patients participate in the determination of the methadone dose and are aware of the dose dispensed. Urine specimens are collected on a weekly basis and are analyzed randomly for morphine and cocaine (so that 2-4 results per month are available). Urine collection is supervised by a nurse to prevent fraud.

As to psychiatric interventions, these are carried out after referral by the physician who is in charge of the patient. Once the patient receives a psychiatric diagnosis, the psychiatrist becomes responsible for the management both of psychiatric intervention and methadone treatment. Standard psychiatric interventions, guaranteed on the premises, include assessment and diagnosis, psychopharmacological treatments and non-specific psychotherapies. Psychopharmacological medications are administered daily in the clinic, or are given to the patient or relatives on the basis of a case-by-case evaluation. Individual psychotherapies carried out by psychiatrists or psychologists are available, independently of the presence of psychiatric comorbidity, as cognitive- or insight-oriented supporting sessions. However, in patients with a double diagnosis, special attention is given to the treatment of issues related to comorbidity.

Patients, instruments and procedure

78 patients who initiated a methadone treatment between August 2000 and May 2001 were included in the study. The mean age was 33.7 years (SD 6.6); 91% were males and 9% females; 75.6% were single and 24.4% married; 44 were employed and 34 unemployed. 25% had completed fewer than eight years of education and 75% eight years or more; the average length of opioid addiction was 10.2 years (SD 5.3).

The assessment instruments at baseline included the Addiction Severity Index interview (ASI), the Symptoms Check List (SCL-90), the Beck Depression Inventory (BDI) and an Analogue Visual Craving Scale (AVCS). SCL-90 and craving scale were administered again after one month and then every two months. ASI and BDI were readministered after six months. Monthly mean methadone dosages, urinary positivity for opioids and cocaine, psychopharmacological treatment and numbers of interventions were also recorded.

In order to obtain two groups of patients differing in their severity of psychiatric symptomatology, patients were divided into two groups on the basis of their baseline SCL-90 scores; one group included patients with scores of 1.3 or more in at least one SCL-90 sub-scale, while the other included those without any score of 1.3 or more.

These two groups of patients were then compared for socio-demographic, toxicological, psychopathological and treatment-related variables.

Results

Of the 78 patients assessed at baseline, 44% reported at least one SCL-90 score of 1.3 or more and 56% scores that were all below 1.3.

| | Low severity | | High severity | | T | p |
|---------------------------|--------------|------|---------------|------|-------|-------|
| | M | s | m | s | | |
| Years of heroin addiction | 10.10 | 4.9 | 10.40 | 6.0 | 0.24 | ns |
| Heroin craving | 59.60 | 37.7 | 66.50 | 30.5 | 0.84 | ns |
| Cocaine craving | 30.30 | 37.5 | 26.00 | 33.0 | -0.50 | ns |
| Alcohol craving | 4.20 | 9.8 | 7.90 | 16.1 | 1.12 | ns |
| BDI | 12,20 | 8.5 | 26.10 | 12.4 | 1.12 | 0.000 |
| ASI | | | | | | |
| Medical | 0,17 | 0.2 | 0.18 | 0,2 | 0.17 | ns |
| Employment | 0.60 | 0.3 | 0.70 | 0.3 | 1.29 | ns |
| Drugs | 0.34 | 0.1 | 0.39 | 0.1 | 1.80 | ns |
| Alcohol | 0.07 | 0.1 | 0.13 | 0.2 | 1.46 | ns |
| Legal | 0.22 | 0.2 | 0.38 | 0.3 | 2.25 | 0.028 |
| Social | 0.20 | 0.1 | 0.27 | 0.2 | 1.31 | ns |
| Psychic | 0.15 | 0.1 | 0.41 | 0.2 | 5.74 | 0.00 |

The two groups revealed gender-correlated differences. In particular, all the women taking part in the study had an SCL-90 score of 1.3 or higher. The other socio-demographic characteristics showed no differences between the two groups. As regards clinical characteristics too, most of the variables considered showed no statistically significant differences between the two groups (table 1).

BDI (table 1) showed a significantly higher score for patients belonging to the group with severe psychopathology 26.1; (SD = 12.4) than that for the group with milder psychopathology or none at all 12.2; (SD = 8.5); Student's $t = 1.125$; $p = 0.000$. This result was to be expected on the basis of the factor chosen to allow discrimination between the two groups.

The analysis of the baseline psychic ASI composite score (table 1) confirmed the greater psychiatric severity of the group identified on the basis of its higher SCL-90 score 0.41 (SD = 0.20) versus 0.15 (SD = 0.17); $t = 5.743$; $p = 0.000$. The composite score for the ASI legal area also turned out to be higher for patients in the group that had greater problems at the psychiatric level 0.38 (SD = 0.33) versus 0.22 (SD = 0.26); $t = 2.256$; $p = 0.028$.

As regards the treatment received by the two groups of patients (data available only for the first year of the study), there were no significant differences in the numbers of visits: 15.7 (SD = 10.6) in the group with milder psychopathology versus 17.5 (SD = 13.4) in the group with a higher degree of psychopathology (ANOVA one-way: $F =$

Table 2. Baseline-endpoint changes in SCL-90 scores

| | Low severity | | | | | | High severity | | | | | |
|---------------------------|--------------|-----|----------|-----|----------|-----|---------------|-----|-------|-------|------------|-------|
| | Baseline | | Endpoint | | Baseline | | Endpoint | | Time | | Group-Time | |
| | M | s | M | s | M | s | M | s | F | P | F | P |
| Total | 0.44 | 0.2 | 0.35 | 0.2 | 1.29 | 0.4 | 0.66 | 0.5 | 43.82 | 0.000 | 25.50 | 0.000 |
| Anxiety | 0.37 | 0.2 | 0.32 | 0.3 | 1.22 | 0.6 | 0.75 | 0.6 | 12.03 | 0.001 | 8.73 | 0.005 |
| Anger-Hostility | 0.45 | 0.3 | 0.40 | 0.5 | 1.02 | 0.6 | 0.53 | 0.3 | 10.83 | 0.002 | 6.95 | 0.011 |
| Phobis anxiety | 0.06 | 0.1 | 0.13 | 0.3 | 0.50 | 0.4 | 0.17 | 0.2 | 7.61 | 0.008 | 17.88 | 0.000 |
| Paranoidism | 0.42 | 0.3 | 0.31 | 0.2 | 1.07 | 0.5 | 0.62 | 0.4 | 21.66 | 0.000 | 7.99 | 0.006 |
| Psychoticism | 0.04 | 0.2 | 0.29 | 0.3 | 0.92 | 0.5 | 0.52 | 0.5 | 7.71 | 0.070 | 12.08 | 0.001 |
| Somatization | 0.52 | 0.3 | 0.38 | 0.4 | 1.71 | 0.8 | 0.97 | 0.6 | 27.33 | 0.000 | 12.25 | 0.001 |
| Obsessive compulsive | 0.52 | 0.3 | 0.46 | 0.3 | 1.41 | 0.7 | 0.73 | 0.5 | 26.65 | 0.000 | 18.68 | 0.000 |
| Interpersonal sensitivity | 0.35 | 0.3 | 0.29 | 0.2 | 1.10 | 0.7 | 0.52 | 0.5 | 23.45 | 0.000 | 16.15 | 0.000 |
| Depression | 0.55 | 0.3 | 0.43 | 0.3 | 1.65 | 0.6 | 0.92 | 0.7 | 33.80 | 0.000 | 16.79 | 0.000 |

0.403; $p = 0.528$). Psychopharmacological treatments were, in any case, more frequent in patients with more severe psychopathology (57.1% versus 27.1%; Chi square = 6.770; $p = 0.009$).

Retention

Retention in treatment did not differ significantly between the two groups; 55% of the patients with more severe psychopathology proved to be in treatment a year later, against 63% of the patients with milder or no psychopathology. The Kaplan-Mayer survival analysis confirmed the lack of statistically significant differences (Log-Rank test 0,04; $p = \text{NS}$), (Figure 1)

Toxicological urinary results

The difference in the percentages of urinalyses that were positive for opioids was not statistically significant in the two groups of patients. As shown in figure 2, there was a steady fall in the use of heroin, but no statistically significant differences between the two groups of patients emerged. Moreover, analysis of the results obtained by classifying missing urine samples as if they were positive shows a similar profile, with no significant differences between the two groups.

The mean percentage of urinalyses that were positive for cocaine metabolites failed to reveal significant differences between the two groups. Figure 3 shows the results obtained in the first 20 months of treatment.

Methadone dose

Figure 4 shows the variations in methadone dosages during the course of treatment (broken off at 17 months). A tendency for there to be a progressive increase in

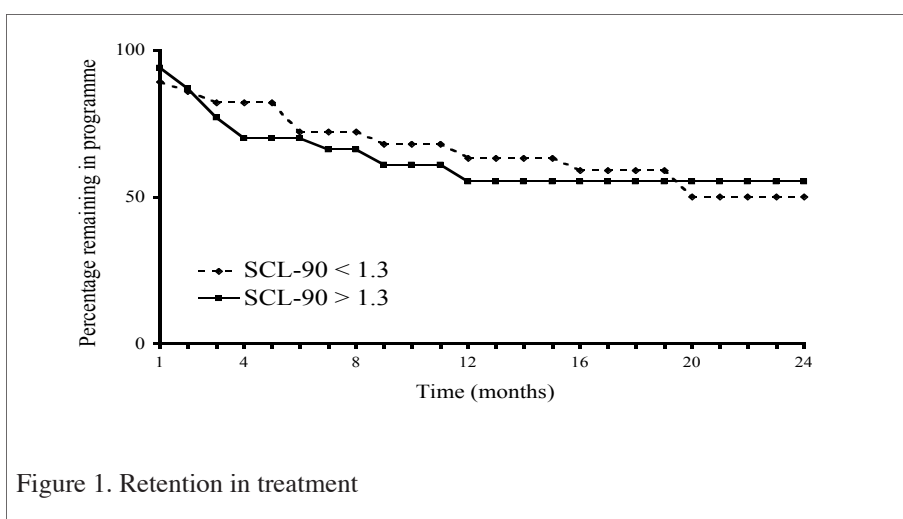


Figure 1. Retention in treatment

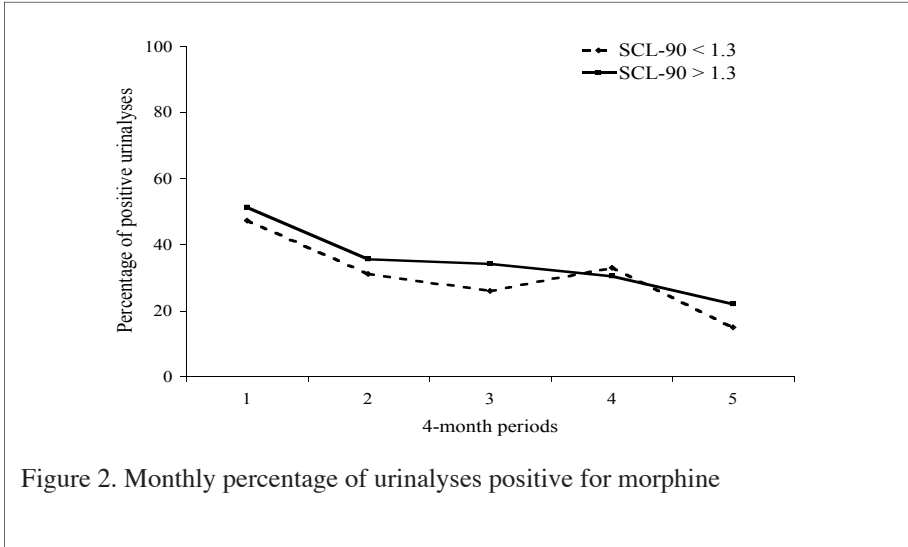


Figure 2. Monthly percentage of urinalyses positive for morphine

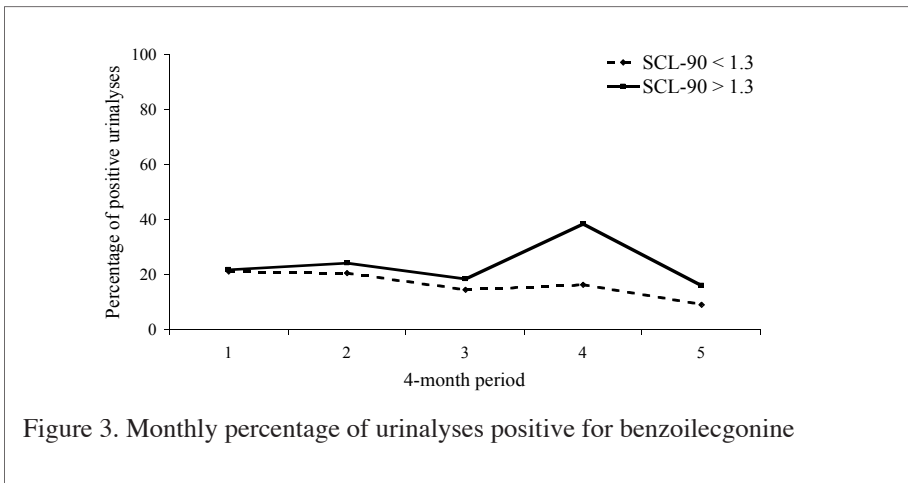


Figure 3. Monthly percentage of urinalyses positive for benzoilecgonine

dosages over time emerges. It can also be seen that patients with greater psychiatric problems show higher mean values. These reach statistical significance in the 5th and 6th months ($p < 0.05$).

When the severity of depressive symptomatology as assessed by the BDI was used to discriminate between the two groups, the patients with the higher scores were those who had taken higher dosages of methadone (figure 5). The differences observed turned out to be statistically significant after the 6th month ($p < 0.05$).

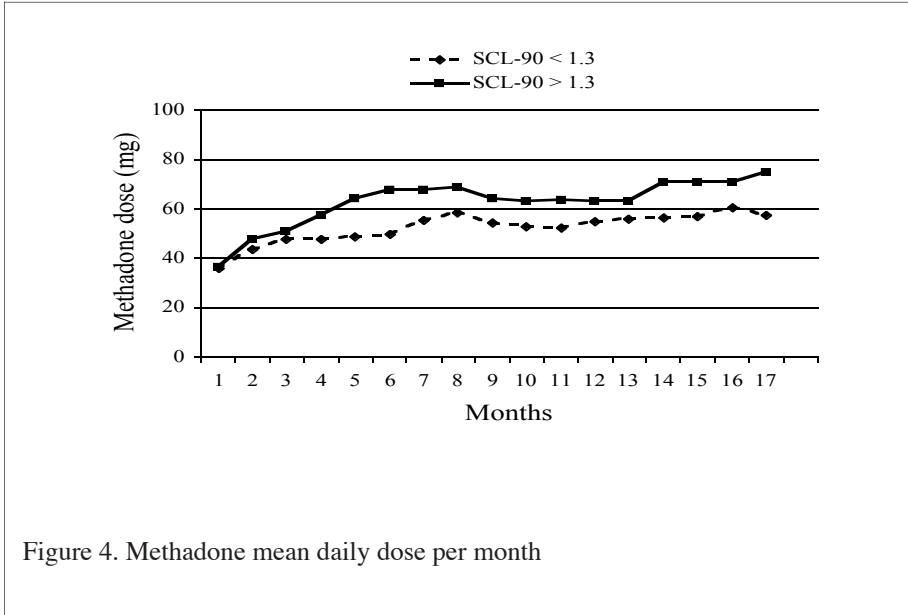


Figure 4. Methadone mean daily dose per month

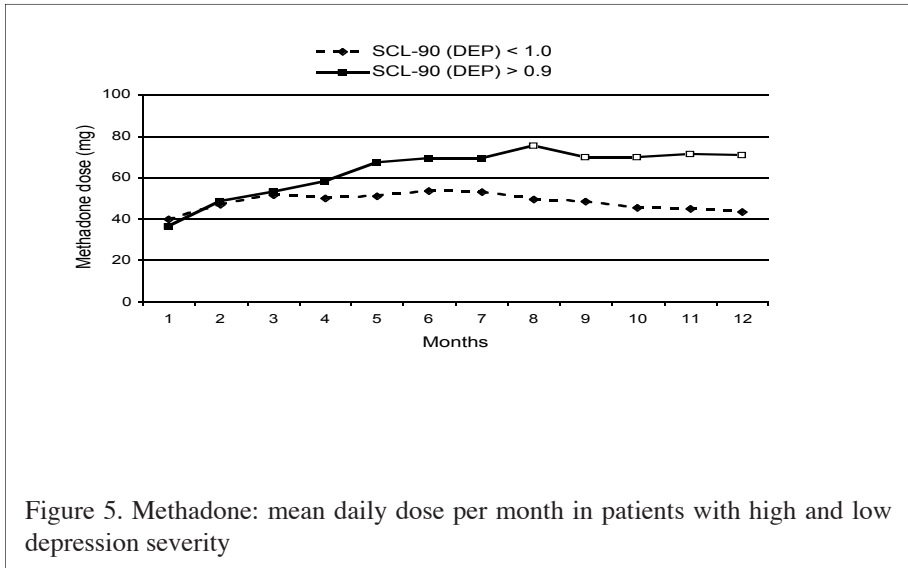


Figure 5. Methadone: mean daily dose per month in patients with high and low depression severity

Psychiatric status

Table 2 shows the variations in SCL-90 scores recorded during the course of treatment. Almost all the psychopathological dimensions explored showed a significant alleviation of symptoms during the course of treatment. Moreover there was a significantly greater

improvement in patients who had a more severe psychopathology.

Discussion

Retention and toxicological results

In our study, the results of methadone maintenance treatment do not substantially differ between patients with marked versus less marked psychiatric severity, either in terms of retention in treatment or of toxicological results (heroin use). A sizeable fall in the use of heroin occurs in both groups, starting in the first month of treatment, and increasing over time.

Our results seem to confirm those reported in previous retrospective ones using the same outcome parameters²². The adoption of a prospective cohort design adds validity to these results, by limiting the risk of a misclassification bias through the use of objective, reliable, reproducible evaluation instruments for the classification of patients on the basis of their psychiatric severity.

Our results agree also with those obtained by Cacciola³, who classified patients on the basis of the presence of a psychiatric diagnosis that adopted DSM-III-R criteria, using the SCID interview.

Methadone dose

The patients characterized by a higher level of psychiatric severity were those who took higher mean methadone dosages, but the differences observed in dosages only reached statistical significance in patients who spent a considerable period in treatment and in those characterized by unusual severe depressive symptoms. These results seem to confirm previous observations on the tendency of dual diagnosis patients to stabilize at higher mean methadone doses^{28,22,16}.

Psychiatric status

Over time, the psychiatric status of both groups of patients seems to improve. Moreover, those displaying a severer psychopathology at the baseline were those who showed a greater fall in symptom severity, so it does seem that the therapeutic programme affects indicators of psychic functioning. These results are consistent with those obtained by Cacciola³.

Interpretative hypothesis

The results of our study partly differ from those obtained in previous studies, which had indicated a generally negative prognostic significance of the presence and severity of psychiatric comorbidity.

One explanation for this discrepancy may be that the patients whose psychiatric problems are the most severe are those who are most affected by the restrictions and limitations usually included in methadone programmes. It is reasonable to think that the adoption of laborious, complicated procedures for access to and maintenance of

treatment may reduce compliance with it and negatively influence its outcome, especially in the case of patients whose psychosocial status is most degraded. The context of the treatment that we considered presents the characteristics of the low threshold programmes, with the aim of reducing to a minimum the procedures and requisites that could exclude or penalize patients with a high degree of psychosocial deterioration.

An alternative hypothesis that could explain our results is the existence of specific psychiatric care within the methadone maintenance programme that we investigated. In our study, patients in the two groups showing different degrees of psychiatric severity did not differ in their retention in treatment or their recourse to abuse substances of abuse, but they did differ in revealing a higher frequency of psychopharmacological treatment in patients who had a more marked psychopathology. This result is in line with a number of studies confirming the efficacy of psychopharmacological as well as psychotherapeutic interventions in treating comorbid psychiatric disorders in addicts^{31,32,30,21}.

One last hypothesis is supported by the higher mean methadone dose taken by patients with greater psychiatric severity: that the efficacy of methadone may apply not only to heroin use, but also to other psychiatric symptoms. The usefulness of methadone and other opioids in psychiatric illnesses has, in fact, been reported by many authors^{4,11,9,8,2,10,1}. However, the observed improvement in psychiatric symptomatology in the course of treatment does not necessarily depend on a specific effect of methadone on specific mental illnesses. It might depend on a capacity to improve the psychic symptoms that are linked with heroin addiction rather than those linked with independent psychopathology. In an attempt to verify this hypothesis, we compared the outcome of patients who took psychiatric medication with the outcome of those who took no such medication. Both groups of patients showed a significant improvement in psychic status, without significant differences.

Independently of the nature of the psychopathology associated with heroin addiction, the hypothesis that methadone affects some psychopathological dimensions is consistent with current neurobiological knowledge which supports the concept that the functioning of the meso-limbic and meso-cortical dopaminergic systems may be involved in specific psychiatric disorders^{33,5,12,13,29}, while it attributes to opioids the capacity to act on this system^{6,7}. In addition, the probably positive influence on psychopathology of the non pharmacological components of the programme and of changes in life-style consequent on discontinuation of heroin use should be taken into account.

Limits

The value of the results obtained must be weighed against some limiting factors: in particular, the low number of patients enrolled and the lack of formal psychiatric diagnoses. The low number of patients could interfere with the evaluation of significant differences among the two groups considered, while the lack of formal psychiatric diagnoses precludes clear distinctions between substance-induced and independent psychiatric disorders.

Conclusions

This research appears to increase the congruency of data showing that even severe psychiatric comorbidity does not substantially alter the efficacy of methadone maintenance treatment. The acquisition of a major degree of certainty as to the efficacy of methadone treatment on populations with psychiatric comorbidity will provide an important stimulus for the extension of maintenance programmes to include the dually diagnosed patient populations.

References

1. Bodkin, J.A., Zornberg, G.L., Lukas, S.E., Cole, J.O., (1995). Buprenorphine treatment of refractory depression. *Journal of Clinical Psychopharmacology* 15 (1), 49-57.
2. Brizer, D.A., Hartman, N., Sweeney, J., Millman, R.B., (1985). Effect of methadone plus neuroleptics on treatment-resistant chronic paranoid schizophrenia. *The American Journal of Psychiatry* 142, 1106-1107.
3. Cacciola, S.J., Alterman, A.I., Rutherford, M.J., McKay, J.R., Mulvaney, F.D., (2001). The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. *Drug Alcohol Depend.* 61, 271-280.
4. Carlson, E.T. and Simpson, M.M., (1963). Opium as a tranquilizer. *The American Journal of Psychiatry*, 112-117.
5. Deutch, A.Y., (1992). The regulation of subcortical dopamine system by the prefrontal cortex: interactions of central dopamine systems and the pathogenesis of schizophrenia. *Journal of Neural Transmission. Supplementum* 36, 61-89.
6. Di Chiara, G. and Imperato, A., (1998). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences of the United States of America* 85, 5274-5278.
7. Di Chiara, G. and Imperato, A., (1998). Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. *The Journal of Pharmacology and Experimental Therapeutics* 244, 1067-1080.
8. Emrich, H.M., Vogt, P., Herz, A., (1982). Possible antidepressive effects of opioids: action of buprenorphine. *Annals of the New York Academy of Sciences* 398, 108-112.
9. Exstein, I., Pickar, D., Gold, M.S., Gold, P.W., Pottash, A.L.C., Sweeney, D.R., Ross, R.J., Rebard, R., Martin, D., Goodwin, F.K., (1981). Methadone and morphine in depression. *Psychopharmacology Bulletin* 17, 29-33.
10. Feinberg, D.T. and Hartman, N., (1991). Methadone and schizophrenia letter. *The American Journal of Psychiatry* 148, 1750-1751.
11. Fink, M., Simeon, J., Itil, T.M., Freedman, A.M., (1970). Clinical antidepressant activity of cyclazocine - a narcotic antagonist. *Clinical Pharmacology and*

- Therapeutics 11, 41-48.
12. Grace, A.A., (1991). Commentary. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* 41 (1), 1-24.
 13. Kahn, R.S. and Davis, K.L., (1995). New developments in dopamine and schizophrenia. In: F.E. Bloom and D.J. Kupfer (Eds.) *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press.
 14. Kosten, T.R., Rounsaville, B.J., Kleber, H.D., (1986). A 2.5-year follow-up of depression, life crises, and treatment effects on abstinence among opioid addicts. *Arch. Gen. Psychiatry*. 43, 733-738.
 15. LaPorte, D.J., McLellan, A.T., O'Brien, C.P., Marshall, J.R., (1981). Treatment response in psychiatrically impaired drug abusers. *Compr. Psychiatry*. 22 (4), 411-419.
 16. Marenmani, I., Zolesi, O., Aglietti, M., Tagliamonte, A., Shinderman, M., Maxwell, S., (2000). Methadone dose and retention during treatment of heroin addicts with Axis I psychiatric comorbidity. *J Addict Dis* 19 (2), 29-41.
 17. McLellan, A.T., Woody, G.E., Luborsky, L., O'Brien, C.P., Druley, K.A., (1983). Increased effectiveness of substance abuse treatment: a prospective study of patient-treatment matching. *J. Nerv. Ment. Dis.* 171, 597-605.
 18. McLellan, A.T., Luborsky, L., Woody, G.E., Druley, K.A., O'Brien, C.P., (1983). Predicting response to alcohol and drug abuse treatments: role of psychiatric severity. *Arch. Gen. Psychiatry*. 40, 620-625.
 19. McLellan, A.T., Luborsky, L., O'Brien, C.P., (1986). Alcohol and drug abuse treatment in three different populations: is there improvement and is it predictable? *Am. J. Drug Alcohol Abuse*. 12, 101-120.
 20. McLellan, A.T., (1986). "Psychiatric severity" as a predictor of outcome from substance abuse treatments. In: *Psychopathology and Addictive Disorders* (Meyer, R.E., ed.) Guilford Press, New York.
 21. Nunes, E.V., Quitkin, F.M., Brady, R., Steward, J.W., (1991). Imipramine treatment of methadone maintenance patients with affective disorder and illicit drug use. *Am. J. Psychiatry*. 148 (5), 667-669.
 22. Pani, P.P., Trogu, E., Contu, P., Agus, A., Gessa, G.L., (1997). Psychiatric severity and treatment response in a comprehensive metadone maintenance treatment program. *Drug Alcohol Depend*. 48, 119-126.
 23. Pani, P.P., Agus, A., Gessa, G.L., (1999). Methadone as a mood stabilizer. *Her. Addict. Relat. Clin. Probl.* 1(1), 43-44.
 24. Rounsaville, B.J., Weissman, M.M., Crits-Cristoph, K., Wilber, C.H., Kleber H.D., (1982). Diagnosis and symptoms of depression in opiate addicts: course and relationship to treatment outcome. *Arch. Gen. Psychiatry*. 39, 151-156.
 25. Rounsaville, B.J., Tierney, T., Crits-Christoph, K., Weissman, M.M., Kleber, H.D., (1982). Predictors of outcome in treatment of opiate addicts: evidence for the multidimensional nature of addicts' problems. *Compr. Psychiatry*. 23 (5),

- 462-478.
26. Rounsaville, B.J., Kosten, T.R., Weissman, M.M., Kleber, H.D., (1986). Prognostic significance of psychopathology in treated opioid addicts: a 2.5-year follow-up study. *Arch. Gen. Psychiatry.* 43, 739-745.
 27. State Methadone Maintenance Treatment Guidelines, (1992). U.S. Department of Health and Human Services. Public Health Service. Substance Abuse and Mental Health Services Administration, Rockville.
 28. Treece, C.D. and Nicholson, B., (1980). DSM-III personality type and dose levels in methadone maintenance patients. *J. Nerv. Ment. Dis.* 168 (10), 621-629.
 29. Willner, P. (1995). Dopaminergic mechanisms in depression and mania. In: F.E. Bloom & D.J. Kupfer (eds.) *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press.
 30. Woody, G.E., O'Brien, C.P., Rickels, K., (1975). Depression and anxiety in heroin addicts: a placebo-controlled study of doxepin in combination with methadone. *Am. J. Psychiatry.* 132, 447-450.
 31. Woody, G.E., O'Brien, C.P., McLellan, A.T. et al., (1982). The use of antidepressants with methadone in depressed maintenance patients. *Ann. N.Y. Acad. Sci.* 398, 120-127.
 32. Woody, G.E., McLellan, A.T., Luborsky, L., O'Brien, C.P., Blaine, J., Fox, S., Herman, I., Beck, A.T., (1984). Psychiatric severity as a predictor of benefit from psychotherapy: The Penn-VA study. *Am. J. Psychiatry.* 141 (10), 1172-1177.
 33. Wong, D.F.; Wagner, H.N.; Tune, N.E.; Dannais, R.F.; Pearson, G.D.; Links, J.M.; Tamminga, C.A.; Broussolle, E.P.; Ravert, H.T. & Wilson, A.A. (1986). Positron emission tomography reveals elevated D2 dopamine receptors in drug naive schizophrenics. *Science* 234 (4783): 1558-1563.

Received May 30, 2003 - Accepted September 15, 2003