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Research report

The long-term outcomes of heroin dependent-treatment-resistant patients with bipolar 1 comorbidity after admission to enhanced methadone maintenance

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ABSTRACT

Objective: The aim of this study was to compare the long-term outcomes of treatment-resistant bipolar 1 heroin addicts with peers who were without DSM-IV axis I psychiatric comorbidity (dual diagnosis).
Method: 104 Heroin-dependent patients (TRHD), who also met criteria for treatment resistance – 41 of them with DSM-IV-R criteria for Bipolar 1 Disorder (BIP1-TRHD) and 63 without DSM-IV-R axis I psychiatric comorbidity (NDD-TRHD) – were monitored prospectively (3 years on average, min. 0.5, max. 8) along a Methadone Maintenance Treatment Programme (MMTP).
Results: The rates for survival-in-treatment were 44% for NDD-TRHD patients and 58% for BIP1-TRHD patients ($p=0.062$). After 3 years of treatment such rates tended to become progressively more stable. BIP1-TRHD patients showed better outcome results than NDD-TRHD patients regarding CGI severity ($p<0.001$) and DSM-IV GAF ($p<0.001$). No differences were found regarding urinalyses for morphine between groups during the observational period. Bipolar 1 patients needed a higher methadone dosage in the stabilization phase, but this difference was not statistically significant.
Limitations: The observational nature of the protocol, the impossibility of evaluating a follow-up in the case of the patients who dropped out, and the multiple interference caused by interindividual variability, the clinical setting and the temporary use of adjunctive medications.
Conclusions: Contrary to expectations, treatment-resistant patients with bipolar 1 disorder psychiatric comorbidity showed a better long-term outcome than treatment-resistant patients without psychiatric comorbidity.

1. Introduction

Bipolar spectrum disorders and addiction often co-occur and constitute reciprocal risk factors (Bahorik et al., 2013; Hoblyn et al., 2009; Reif et al., 2011; Schneier et al., 2010) that we believe are best considered from a unified perspective (Maremmani et al., 2006). We studied the correlation between bipolar spectrum and heroin addiction at various levels. In our in-patient setting we found that a majority of our heroin addicts were affected by bipolar 1 disorder (Maremmani et al., 2000), whereas in our outpatient setting they obtained a diagnosis of bipolar 2 disorder (Maremmani et al., 1994). We found that depression and hostility as part of the bipolar spectrum – in the context of early-onset drug dependence, work and social-leisure problems – appear to be independently associated with suicidal ideation. (Maremmani et al., 2007a). We also found that subthreshold bipolarity, including hyperthymic and cyclothymic temperaments, seems to predispose patients to heroin addiction (Maremmani et al., 2009), but craving for the suppressed hypomania could, in its turn, lead to cocaine abuse, which eventually unmasks a frankly bipolar disorder – in some cases leading to mixed state, severe mania, or even to psychosis beyond mania (Maremmani et al., 2008). We also studied clinical presentations of substance abuse in bipolar

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heroin addicts at time of treatment entry. Besides one expected result – the prominent use of CNS stimulants during a depressive phase of bipolar patients – this study supports the hypothesis that mood elation is a pleasurable, rewarding experience that, in bipolar patients, can be started or prolonged by means of CNS stimulant drugs. Stimulant use was, therefore, more prevalent during the 'up' rather than the 'down' phase of the illness (Maremmani et al., 2012c). In conclusion, we are aware that the use of substances worsens the therapeutic outcome of bipolar patients (Camacho and Akiskal, 2005; Maj et al., 2003; Mazza et al., 2009; van Rossum et al., 2009). Agonist Opioid Treatment improves symptoms of psychopathology present in patients addicted to heroin (Maremmani et al., 2007b; Pani et al., 2000). In this perspective, we can assume that opiates // are an effective treatment in bipolar patients heroin addicts.

The aim of this study was to compare the long-term outcomes of treatment-resistant, heroin-dependent patients (HD) with bipolar 1 (BIP1-HD) ones, and patients without DSM-IV axis 1 psychiatric comorbidity (NDD-HD). We decided to evaluate whether comorbid psychopathology was able to influence methadone treatment outcomes in patients who had previously failed in first-line, low threshold treatment facilities, when those patients were included in a high-threshold, maintenance-oriented, high-dose methadone programme.

The hypothesis of the study was that DSM-IV bipolar 1 psychiatric comorbidity would not affect treatment outcomes if patients with comorbid disorders received higher, individualized doses of methadone and that a favourable outcome would be related to long-term ongoing treatment (retention).

To test this hypothesis, a group of treatment-resistant heroin addicts, with bipolar 1 or without DSM-IV axis I psychiatric comorbidity, were followed in a naturalistic approach for a minimum of 0.5 and a maximum of 8 years in the context of the maintenance high-threshold, high-dose Pisa methadone programme, using retention in treatment and rates of heroin use as the main end-point parameters.

2. Methods

2.1. Design of the study

A prospective cohort study was designed in order to evaluate treatment outcome (in terms of retention in treatment, substance use, clinical improvement and general social adjustment) of patients included in a methadone programme, in terms of its relationship to the presence of a bipolar 1 psychiatric comorbidity. Treatment-resistant, heroin-dependent patients (TRHD) were divided into two groups – those with bipolar 1 psychiatric comorbidity (BIP1-TRHD patients) and those without concomitant DSM-IV axis I psychiatric disorders (NDD-TRHD patients).

All 104 consecutive patients were admitted to the programme over an 8-year time period (from January 1995 to May 2003) and followed for up to 8 years. The length of the prospective observation was 3 years on average (min. 0.5, max. 8); follow-up evaluation was carried out monthly, from the beginning of treatment.

All patients gave their written informed consent to the study after the procedure had been fully explained. Both the consent form and the experimental procedures were approved by the pertinent ethics committees, in accordance with internationally accepted criteria for ethical research.

2.2. Setting

In Italy, low-threshold facilities for drug addicts are available in each territorial district. In those settings, when opioid agonists are employed, dosage and duration of treatment are usually limited, regardless of clinical indication (Salamina et al., 2010; Schifano et al., 2006), which suggests the value of increased dosage or treatment duration (Brady et al., 2005; D'Ippoliti et al., 1998; Faggiano et al., 2003; Pollack and D'Aunno, 2008). Patients are allowed to negotiate the lowering of dosages regardless of urinalyses, and to have their medication tapered earlier than advisable on the basis of the scientific literature.

All the patients participating in the study were recruited from the Pisa Methadone Maintenance Treatment Programme (Pisa-MMTP), which belongs to the Pisa University Department of Psychiatry. Since 1993, the Pisa-MMTP has been using a clinical protocol that has the characteristics of a high-threshold treatment facility for opioid addiction focusing on pharmacological maintenance. After patients at the Pisa-MMTP have been safely inducted into treatment with methadone, their doses are gradually increased until the point is reached where there is no more than one urine drug screen which is positive for illicit opiates, cocaine, or benzodiazepines in the previous 60-day period.

Once this requirement is fulfilled, the patient is defined as having being "stabilized", and the dose at which this goal has been accomplished is referred to as the "stabilization dose". No upper limit for dosage exists. Nevertheless, one time limitation is present in this setting: patients who cannot achieve stabilization within one year are terminated, to be transferred to local treatment units. The dosage is increased to reflect the results of urinalyses, and evidence of improvement on social grounds is not enough by itself to justify dose stability as long as the urinalyses stay positive for opiates. Patients are not allowed to raise or lower the dose by themselves. Take-home doses, without limitations, and at most for a 7-day period, are allowed, once patients have shown complete compliance with the rules of the programme. Urine samples for toxicology analyses are collected randomly almost once a month, to allow evaluation of the metabolites of illicit drugs and benzodiazepines.

In our programme patients are required to be actively involved in treatment by attending the clinic whenever that is scheduled, participating in the development of their treatment plan, working towards treatment goals, meeting with medical and case management staff, and attending groups when needed.

Patients with psychiatric comorbidity are also treated with psychoactive drugs (mood stabilizers, antipsychotics or antidepressants) and supportive psychotherapy, as needed. All physicians working in the Pisa-Methadone Programmes are psychiatrists who have been trained for at least two years in the treatment of addictive disorders.

2.3. Subjects

All heroin-dependent patients with bipolar 1 psychiatric comorbidity or without psychiatric comorbidity referred to the Pisa-MMT programme during the January 1995–May 2003 period ($N=104$) were consecutively enroled in the study.

To be referred to the Pisa-MMT programme, patients should have:

(1) A diagnosis of heroin dependence according to DSM-IV criteria. We selected those with bipolar 1 psychiatric comorbidity (BIP1-TRHD patients) and those without concomitant DSM-IV axis I psychiatric disorders (NDD-TRHD patients). Axis II diagnoses were excluded from the study, since a wide range of personality disorders are usually displayed by substances abusers, which makes it is very difficult to define axis II diagnostic subgroups.
(2) Resistance to previous first-line, low-threshold methadone treatment programmes attended at local Addiction Treatment Units.