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Association between serum concentration of natriuretic peptides and perceived withdrawal symptoms in opiate maintenance

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Summary

Background: Volume-regulation peptides indirectly influence the hypothalamic–pituitary–adrenal (HPA) axis and thereby also the strength of craving, withdrawal symptoms and the potential risk of relapse. Aims: The primary objective of the present study was to examine the serum levels of atrial and brain natriuretic peptides (ANP and BNP) in patients undergoing different opiate-based maintenance treatments. Methods: We compared two groups of patients receiving levomethadone (n=55) or else diamorphine (n=28) treatment, with a third, healthy control group (n=51). Results: We found a potential association between withdrawal symptoms measured with the Short Opiate Withdrawal Scale (SOWS) and serum levels of ANP and BNP in opiate-addicted patients undergoing diamorphine maintenance treatment. Conclusions: Differently from methadone maintenance, diamorphine seems to be unable to suppress natriuretic peptides levels, which, in our patients, reflect the amount of opioid withdrawal symptomatology.

Key Words: atrial natriuretic peptide; brain natriuretic peptide; diamorphine; natriuretic peptides; opiate dependence; opiate maintenance treatment.

1. Introduction

Natriuretic peptides (NPs), such as atrial and brain natriuretic peptides (ANP and BNP), maintain the circuitry between extracellular fluid volume and blood pressure, regulating the cardiovascular homeostasis. The primary physiological role of NPs like ANP and BNP is to decrease arterial blood pressure by reducing blood volume and systemic vascular resistance. Furthermore, NPs are thought to be involved in the development of psychiatric disorders, including addiction disorders. Volume-regulation peptides, for example vasopressin and ANP, indirectly influence the hypothalamic–pituitary–adrenal (HPA) axis and thereby also the strength of craving, withdrawal symptoms and the potential risk of relapse [10, 12]. Gianoulakis et al. [6] showed increased ANP plasma levels in healthy men after a low dose acute alcohol intake, whereas patients in detoxification treatment showed lower plasma levels of ANP than healthy controls [9, 11]. In addition to these findings based on human studies, there are relevant results from animal experiments. In mice, intraperitoneal administration of ANP decreased anxiety behaviour during alcohol withdrawal [23]. Likewise, natriuretic peptide receptor-A in mice showed a stress-related upregulation correlating with alcohol intake and increased withdrawal symptoms [16]. The existing literature mainly concerns chronic alcohol consumption. Azorov and colleagues [1] considered yet a different effect of ANP injection in mice, looking at the development of tolerance and dependence on morphine. Intracerebroventricular injection of ANP blocked the development of chronic morphine tolerance, but did not
affect the emergence of naloxone-precipitated withdrawal symptoms. Furthermore, prenatal exposure to morphine alters cardiac production, and possibly the release, of both peptides [3].

As primary aim, we assessed the correlation between natriuretic peptides serum concentration and opioid withdrawal symptoms perception in two subgroups of opioid dependent patients under methadone and diamorphine. As secondary aim, we compared peptides levels of both patient subgroups with those of a control group, in order to understand to what extent peptides serum concentration reflect opioid withdrawal symptomatology.

To the best of our knowledge, this is the first study investigating differences in ANP and BNP serum concentrations in patients undergoing different opiate-based maintenance treatments.

2. Methods

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Hannover Medical School, Germany. All patients and healthy controls gave their written informed consent after the procedure had been fully explained to them, but prior to their inclusion in the study.

2.1. Patients and controls

We conducted a prospective study, including two subgroups of opiate-dependent patients and a healthy control group. All patients fulfilled the diagnostic criteria of opiate dependence according to the ICD-10 (International Classification of Diseases, 10th revision) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition). In one group, we investigated 55 opiate-dependent outpatients receiving LEV maintenance treatment, in the other subgroup we examined 28 outpatients participating in a DAM maintenance programme. Furthermore, we included 51 age- and gender-matched, healthy controls. Controls did not suffer from any psychiatric disease or substance misuse, based on questionnaires about their substance consumption. Blood samples were taken in patients and controls in the morning between 8 and 10 a.m. In the opiate-dependent patients, blood samples were taken two hours after intake of DAM or LEV.

2.2. Psychiatric assessment

Sociodemographic data were collected using a structured interview, whose 16 items included family status, ethnic affiliation, academic and occupational development, living and working conditions, and state of health.

All patients provided answers to a test battery, including the following psychiatric assessments:

- **Beck’s Depression Inventory (BDI-II):** Depressive symptoms in patients and control were assessed using the German version [13, 15].
- **Heroin Craving Questionnaire (HCQ):** This multidimensional questionnaire includes 45 items rated on a 7-point scale ranging from ‘strongly disagree’ to ‘strongly agree’. Scoring is done with 5 theory-derived subscales, measuring different aspects of craving [20].
- **Short Opiate Withdrawal Scale (SOWS):** This 10-item scale assesses symptoms of opioid withdrawal on a 4-point intensity scale ranging from ‘none’ to ‘severe’ [8].
- **Visual Analogue Scales (VAS):** Patients rated their current state of heroin craving on a 100-mm horizontal line labelled from ‘no craving at all’ to ‘very strong craving’. Furthermore, participants responded to a 100-mm mood VAS (“How is your general mood right now?”) anchored with a sad face at the left end and a happy face at the right end.

2.3. ANP and BNP serum levels

ANP and BNP serum levels were investigated in the morning, two hours after the administration of LEV or DAM. The individual dosages of the agonist opioid medication were not altered for the study.

The EDTA blood samples and serum aliquots were stored at −80° C immediately after collection. All serum levels were assessed using the DuoSet enzyme-linked immunosorbent assay (ELISA). All of the assays were performed according to the manufacturer’s description. The lower limit of determination was 5 pg/ml for BNP and 10 pmol/L for ANP. The intra-assay and interassay coefficients of variation were CV<1.2-4.2% and CV1.6-4.6% for BNP; and CV<2.5% and CV6.5% for ANP.

2.4. Statistical analysis

Deviation from the normal distribution was tested using the Kolmogorov-Smirnov test. For BNP serum levels, we found a normal distribution, but not for ANP serum levels. Therefore, ln-transformation was applied to ANP serum levels in order to attain a normal distribution. After that, parametric meth-
Association between serum concentration of natriuretic peptides and perceived withdrawal symptoms in opiate maintenance

ods were applied. To analyse differences in ANP and BNP serum levels, participants were divided into three subgroups (DAM, LEV and controls). Between-group differences in ANP and BNP serum levels were measured using analysis of variance (ANOVA). Possible associations between psychometric opioid withdrawal symptoms and ANP and/or BNP serum levels were investigated using Pearson's correlation coefficient. Linear regression analyses were applied to demonstrate the influence of the SOWS scale on opioid withdrawal symptoms using ANP and BNP serum levels, age, converted methadone dose and alcohol use as independent factors.

Results are presented as mean ± SD (standard deviation); p-values of less than 0.05 (two-tailed) were considered to indicate statistical significance. Data were analysed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp.). Data are presented here using Graph Pad Prism 6 (Graph Pad Inc., San Diego, CA).

3. Results

The characteristics of the two patient subgroups and the control group are shown in Table 1.

### Table 1. Sample characteristics of the subgroups

<table>
<thead>
<tr>
<th>Characteristics: Mean (SD)</th>
<th>DAM (n=28)</th>
<th>LEV (n=55)</th>
<th>Controls (n=51)</th>
<th>Test statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP serum level [pmol/l]</td>
<td>4.04 (0.49)</td>
<td>3.92 (0.48)</td>
<td>3.73 (0.40)</td>
<td>F=3.392A</td>
<td>0.037</td>
</tr>
<tr>
<td>BNP serum level [pg/ml]</td>
<td>197.95 (257.24)</td>
<td>112.22 (86.58)</td>
<td>61.18 (62.65) F=6.058A</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age [yrs]</td>
<td>41.68 (7.91)</td>
<td>37.65 (7.45)</td>
<td>40.37 (9.65)</td>
<td>F=1.290A</td>
<td>n.s.</td>
</tr>
<tr>
<td>Women (%)</td>
<td>14.29</td>
<td>36.36</td>
<td>45.1</td>
<td>F=6.024A</td>
<td>0.003</td>
</tr>
<tr>
<td>Body-mass index [kg/m²]</td>
<td>25.86 (5.04)</td>
<td>23.79 (3.95)</td>
<td>24.96 (3.38)</td>
<td>F=2.492A</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at first drug use [yrs]</td>
<td>18.21 (4.05)</td>
<td>17.18 (4.83)</td>
<td></td>
<td>F=3.075t</td>
<td>n.s.</td>
</tr>
<tr>
<td>Converted methadone dose [mg]</td>
<td>130.36 (31.74)</td>
<td>86.67 (41.38)</td>
<td></td>
<td>F=0.363t</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alcohol use [g/day]</td>
<td>24.57 (34.89)</td>
<td>50.15 (73.87)</td>
<td></td>
<td>F=3.173t</td>
<td>n.s.</td>
</tr>
<tr>
<td>Medication use (%)</td>
<td>100</td>
<td>96.4</td>
<td></td>
<td>F=50.576t</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco (%)</td>
<td>100</td>
<td>96</td>
<td></td>
<td>F=0.004t</td>
<td>n.s.</td>
</tr>
<tr>
<td>Amphetamine (%)</td>
<td>10.9</td>
<td>46.4</td>
<td></td>
<td>F=40.679t</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cocaine (%)</td>
<td>70.9</td>
<td>89.3</td>
<td></td>
<td>F=17.133t</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cannabis (%)</td>
<td>50.9</td>
<td>92.9</td>
<td></td>
<td>F=145,891t</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ecstasy (%)</td>
<td>3.6</td>
<td>46.4</td>
<td></td>
<td>F=158,000t</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crystal meth (%)</td>
<td>1.8</td>
<td>7.1</td>
<td></td>
<td>F=6.015t</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*Drug co-use besides substitute in the last 4 weeks before survey; DAM = diamorphine; LEV = levomethadone; A = analysis of variance; t = t-value.*

Pearson correlation analysis showed a significant correlation between the SOWS cumulative value in the DAM group, and the ANP and BNP serum levels in the DAM group (ANP: r=0.478, p<0.01; BNP: r=0.525, p<0.01) (Figure 1). Furthermore, we found significant correlations for the subscale for lacrimation on the SOWS (ANP: r=0.503, p<0.01; BNP: r=0.391, p=0.040), subscale for yawning (ANP: r=0.474, p=0.011; BNP: r=0.643, p=0.01), subscale for muscle tension (ANP: r=0.415, p=0.028; BNP: r=0.557, p<0.01), subscale for pальitation (BNP: r=0.419, p=0.026) and subscale for muscle twitching (BNP: r=0.425, p=0.024) in the DAM group. Bonferroni’s post hoc test was used to determine the significant differences between the three subgroups. We only found statistical significant differences between DAM and controls for ANP (p=0.034), as well as for BNP (p=0.004) serum levels. Means between DAM and LEV and means between LEV and controls failed to show any significant differences.

In the LEV group, we found no associations between ANP or BNP serum levels and withdrawal symptoms (SOWS cumulative value and ANP: r=-0.159, p=0.264; BNP: r=-0.188, p=0.187).

In addition to these findings, neither ANP nor BNP serum levels in the DAM group showed significant associations with the daily opiate dose, converted into methadone in milligrams per day (ANP: r=0.239, p=0.221; BNP: r=0.203, p=0.301), or with the alcohol intake measured in grams per day (ANP: r=0.048, p=0.808; BNP: r=-0.203, p=0.335).
3.2. Group differences in ANP and BNP serum levels

Investigation of between-group differences in ANP and BNP serum levels was performed using analysis of variance (ANOVA), with significant differences shown in Table 1. The DAM group showed the highest ANP and BNP serum concentrations, followed by lower levels in the LEV group. The control group showed the lowest ANP and BNP serum levels.

3.3. Regression analyses

For the purpose of examining the potential influence of natriuretic peptides on withdrawal symptoms of opiate dependence as measured with the SOWS, we performed two linear regression models in the DAM group. In the two constructed linear regression models, we set either ANP or BNP serum levels as an additional independent factor. SOWS were set as the dependent factor. In the first linear regression model we found that the ANP serum levels, age, gender, converted methadone dose and alcohol use accounted for 23% (adjusted R² = 0.225) of the variance in the SOWS cumulative value (F=2.960, p=0.041). In the first regression model, regarding the independent factors, ANP serum levels showed a significant influence (beta coefficient: 0.519, p=0.013). In the second linear regression model, we found that the BNP serum levels, age, gender, converted methadone dose and alcohol use accounted for 24% (adjusted R² = 0.241) of the variance in the SOWS cumulative value (F=3.143, p=0.034). In the second regression model, regarding the independent factors, BNP serum levels showed a significant influence (beta coefficient: 0.497, p=0.010).

4. Discussion

The primary aim of the present study was to investigate a possible association between natriuretic peptides serum concentration and opioid withdrawal symptoms perception in two subgroups of opiate dependent patients under LEV and DAM. In addition, we compared peptides levels patient subgroups with those of a control group. The main results were found in the patient subgroup undergoing DAM maintenance treatment compared to the LEV subgroup and the control group. In the DAM subgroup, we found a potential association between withdrawal symptoms measured with the Short Opiate Withdrawal Scale (SOWS) and serum levels of NP’s. In line with our results, ANP serum levels have been reported to be significantly higher in opiate dependent patients compared to healthy controls [7]. Moreover we found associations between physical withdrawal symptoms (measured with the SOWS) and ANP and BNP serum levels. ANP and BNP are released following stretch-
ing within the cardiac atrium and ventricle in order to regulate cardiovascular homeostasis. We found associations for the SOWS cumulative value and the subscales muscle tension, palpitation and muscle twitching. It is noted that ANP appears to influence the development of tolerance for morphine dependence in mice [1]. Morphine seems to affect brain function to increase plasma levels of ANP. In opiate-dependent patients, DAM injection demonstrated acute effects on HPA axis activity and craving [5]. DAM administration caused a significant decrease in plasma ACTH levels. Because of the acute suppressing effects of DAM injection on the stress response, Gerber and colleagues described DAM as a possible alternative to methadone maintenance in especially stress-sensitive opiate-dependent patients. Regarding the biological effect and the existence of withdrawal phenomena we found in the DAM subgroup, it should be noted, that in our study patients investigated in the DAM subgroup have injected DAM and the LEV subgroup have taken up their opioid agonist as oral agent. In particular, LEV has a longer biological effect on individuals than DAM [2, 18, 22]. However, to date, rarely clinical studies have been conducted in this field, especially investigating differences in the behavioural mode of action of opiate maintenance with different agonist medication. In addition, investigations of subcortical structures in heroin-addicted patients were indicative of associations between negative emotions and heroin use [4, 17]. Comparable to these findings, treatment with oral morphine was associated with lower severity of mental stress symptoms compared to methadone treatment [21]. With regard to our results on opioid withdrawal symptomatology, DAM in the medium-long term, might not totally be able to suppress withdrawal symptoms and natriuretic peptides alteration in the DAM subgroup leads to the phasic nature of its stimulation. To our best knowledge, the longitudinal course of NPs serum levels has not yet been investigated following opiate administration. Research considering long-term opiate maintenance treatment is absent and necessary.

Limitations

The major limitations of our study include the small sample size, the absence of a urine test for drug screening and the simultaneous use of multiple drugs by our participants, the latter problem having already been reported as a common feature in opiate-dependent subjects [14, 19].

5. Conclusions

Our study suggests a potential association between opioid withdrawal symptoms and serum levels of ANP and BNP in opiate-dependent patients undergoing diamorphine maintenance treatment, but not in those in methadone maintenance treatment. Unlike methadone maintenance, maintenance with diamorphine seems to be unable to suppress levels of natriuretic peptides, which, in our patients, reflect the amount of opioid withdrawal symptomatology.

References


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Contributors
All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest
Authors have no conflicts of interests to declare.

Ethics
Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

Note
It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author accepted our service.
Enhancing knowledge and reducing barriers improve hepatitis C management in methadone maintenance treatment patients

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Summary

Background: Lack of knowledge and bureaucratic obstacles may prevent hepatitis C virus (HCV) treatment among methadone maintenance treatment (MMT) patients. Aims: to improve knowledge and enhance HCV treatment. Methods: HCV seropositive patients were invited to attend a lecture on HCV disease. Participants completed Virus-knowledge and Depression questionnaires before and after the lecture, and were then referred to evaluation and treatment in Liver Unit. Results: Of all the 80 eligible patients invited, 48 attended the lecture and scored significantly better on knowledge about HCV than the non-attendees. Having attended a lecture predicted referral to treatment (Odds ratio (OR) = 13 (95% Confidence Interval (CI) 3.9-44.9 P < 0.0005)). Of the 41 referrals, only 21 (51.2%) actually presented at the Liver Unit; they were characterized by lower depression scores (OR=0.2, 95%CI 0.06-0.9 P = 0.03). Despite administrative barriers, 15 (71.4%) underwent evaluation, 12 (80%) initiated anti-HCV treatment with pegylated interferon, ribavirin with (G1) or without (G2 and G3), a first generation protease inhibitor. Nine patients (75%) achieved sustained virologic response (one was a non-responder and two stopped treatment due to adverse events). Of the 59 who were referred, but did not arrive at the Liver Unit, 14 (23.7%) were followed up elsewhere, but only one of them (7.1%) started treatment. Conclusions: The fact of attending a single lecture led to improved knowledge and enhanced HCV treatment initiation among MMT patients, although the attendees and non-attendees alike still continued to show a certain degree of depression. Interventions to reduce administrative barriers and improve patients’ knowledge about HCV disease, together with treatment of depression when needed, are recommended in MMT patients infected with HCV.

Key Words: Methadone maintenance treatment; ignorance; bureaucratic obstacles; hepatitis C virus treatment; collaboration

1. Introduction

Methadone maintenance treatment (MMT) is considered the most effective treatment for opioid addiction [13]. It employs a well-established protocol for reducing opioid use and for lowering the incidence of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections by decreasing intravenous drug use [6, 7, 27,16]. Longer participation in MMT predicts a better outcome [13, 19]. Of the estimated 25,000 opiate-dependent individuals in Israel, about 4,000 are being treated in MMT or buprenorphine clinics.

Although the anti-HCV seroconversion rate (i.e., acquisition of a new HCV infection) during MMT is low [21], HCV seropositivity for HCV is already present in approximately 50% of the patients entering MMT [18].

At the time when we performed the study, treatment of HCV infection consisted of a combination of weekly injected pegylated interferon α (PegIFN-α) and daily oral ribavirin for 24 to 48 weeks, depending on the HCV genotype. In 2011, first generation protease inhibitors (PI) (telaprevir and boceprevir) were...
added to the national health coverage. Triple therapy with pegIFN-α, ribavirin and a PI was reimbursed for naïve patients with genotype 1 if they had a fibrosis score of ≥F2 according to the Metavir system either by a previous liver biopsy or by a noninvasive method (Fibrotest or Fibroscan), or to previous treatment failures with any fibrosis score [28].

It had been shown previously that MMT patients achieve sustained virologic response (SVR) rates similar to those of other patient populations [14, 17]. Despite this positive outcome, they are less likely to have access to HCV treatment [17]. Multiple barriers to HCV treatment have been reported worldwide; for the patient, these include lack of knowledge about HCV, stigma regarding the disease, fear of side-effects, perceived lack of efficacy and specific comorbidities. For instance, psychiatric disorders are common among patients in MMT programmes [2] and have been shown to interfere with successful HCV treatment [25]. In addition, it is well known that treatment with PegIFN-α is associated with significant side-effects, including neuropsychiatric reactions that may adversely affect compliance [24]. For the caregiver, perceived stigma and lack of knowledge may prevent them from referring substance users to evaluation for anti-HCV treatment [1, 26].

To improve the referral of MMT patients to IFN-based therapy for HCV, we established collaboration between the MMT clinic and the Liver Unit. Selected MMT patients (those positive to an anti-HCV test who were also compliant with maintenance treatment) were invited to attend a lecture about HCV treatment and were then referred to the Liver Unit for evaluation and treatment. The current report analyses barriers to and predictors of HCV treatment initiation, adherence and outcomes during the programme.

2. Methods

The study was approved by the institutional review board, and patients signed an informed consent document.

2.1. Study population

The MMT clinic treats ~330 opioid dependence (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM IV-TR]) adults (≥18 years). The individuals are self-referred or have been referred by various medical or community services. Characterizations of these patients and the clinic’s infrastructure had already been reported [19]. In brief, on admission patients pledge to undergo blood tests for HCV, hepatitis B virus (HBV) and HIV. The patients are tested for HCV antibodies using the Abbott AXSYM System, USA. Tests are carried out at the time of admission and annually. Observed and random urine tests for opiates, a cocaine metabolite (benzoylecgonine), THC, benzodiazepine, amphetamines, are performed on average 2-4 times per month throughout each patient’s course of treatment [19].

Patients receive the methadone orally daily at the clinic, but can achieve the “privileges” of methadone take-home doses based on stable dose, substance abstinence and adequate behaviour [22]. The patients’ demographic and addiction history data were collected from their charts, which also contained a modified Addiction Severity Index (ASI) questionnaire [15].

2.2. Study inclusion criteria

Patients in the MMT programme with a positive anti-HCV test were included if they were compliant with maintenance treatment (daily stable methadone dose) and had been abstinent for at least 3 months, without active psychosis or major depression.

2.3. Instruments

Two questionnaires were used:

1. The 24-item HCV knowledge questionnaire [5] includes several domains (route of HCV transmission, HCV diagnosis and treatment) with True/False/Don’t Know answers. Scores were calculated on the basis of the total number of correct answers (range: 0 to 24). Reliability (Cronbach α) in the current study was 0.73 before the lecture and 0.86 afterwards.

2. The Centre for Epidemiologic Studies Depression (CES-D) questionnaire for mood is a 20-item self-reported scale that assesses aspects of depressive mood that occurred during the previous week [23]. Responses are recorded on a 4 Likert scale from ‘rarely or never’ to ‘most of the time or constantly’. The final CES-D score is the mean of the 20 responses.

2.4. Procedure

In 2012, 158 of the 330 patients treated in the clinic were HCV antibody positive, and 80 of them met the inclusion criteria. Between September 2012 and January 2013, all these 80 patients were invited to attend a lecture given by hepatologists in the MMT clinic. The lectures were performed in small groups.
(19-23 patients), in either Hebrew or Russian (according to the preference of each group). Questionnaires designed to assess each patient’s knowledge about HCV disease and obtain a depression score were completed before and after the lecture, by both attendees and non-attendees. Following the lecture, the patients were referred for a routine evaluation and treatment in accordance with national practices at the Liver Unit. They were first tested for HCV RNA using the HCV COBAS Taqman Test (Roche, Molecular System, Pleasanton, CA) with a lower limit of quantification of 25 IU/mL, to confirm an active HCV infection. The patients received intensive support from the staff of both the MMT clinic and the Liver Unit in overcoming the administrative barriers during the evaluation, treatment initiation and treatment process. Specifically, the staff assisted them in arranging appointments with the Liver Unit, and in coordinating and making contact with their community physician to get the necessary insurance approvals for pretreatment evaluations and the treatment process, while also helping patients navigate to contact the MMT clinic or Liver Unit staff (physician, social worker, nurse) according to their specific needs.

2.5. Data analysis

The chi square test was used for categorical variables, and an analysis of variance (ANOVA) for continuous variables. Repeated measures relying on multivariate analyses were used to detect changes over time in relevant group variables. Logistic regression was used for multivariate analyses for dichotomous variables (i.e., attendance/non-attendance), including significant variables in univariate analyses (P < 0.05). The Pearson correlation coefficient was used to measure linear correlations between continuous variables.

3. Results

3.1. Patients’ characteristics

Eighty patients who fulfilled the study entry criteria were invited to the lectures. Mean age of patients was 47.1 ± 8.4 years, and 17 (21.3%) were females. Mean age at onset of opioid use was 20.6 ± 5.6 years, the mean duration of opioid use before admission to MMT was 18.4 ± 9.1 years. Mean age at admission to MMT was 39.0 ± 8.8 years and the treatment period in the MMT prior to the lecture was 8.5 ± 5.3 years. The patients had a mean of 10.2 ± 3.0 years of education. Slightly over half (52.5%) of the group were Israeli-born and 40% were immigrants from the former USSR. Forty-eight (60%) had children, 26 (32.5%) were married or in a relationship, and 54 (67.5%) lived alone (divorced/widowed). Seventy-two (90%) were former intravenous drug users. Six (7.5%) were also co-infected with HIV and 1 (1.3%) was co-infected with HBV. On admission to the MMT clinic, in addition to their opioid use, 57% of the patients tested positive to benzodiazepine, 32.9% to cocaine, 12.7% to cannabis and 6.6% to amphetamines.

3.2. Knowledge and depression

All the 80 patients filled in questionnaires before and again after the lecture (or at the scheduled time for the lecture, if not attended). Following the lecture, the knowledge score increased significantly among the 48 patients who attended (from 14.9 ± 2.6 to 18.1 ± 2.3) but not among the 32 non-attendees (from 14.2 ± 3.4 to 15.8 ± 3.4, repeated measure, Time*Group F=8.1, P = 0.006, Group F=6.4, P = 0.01). Scores before and after the lecture were linearly correlated (R=0.6, P < 0.0005). The knowledge scores were linearly correlated with the years of education (before lecture: R=0.2, P = 0.03, after lecture: R=0.3, P = 0.007), and inversely correlated (as a trend before and significantly after the lecture) with age (before: R=-0.2, P = 0.1, after: R=-0.35, P = 0.001) and duration of opioid use (R=-0.2, P = 0.07, after: R=-0.41, P < 0.0005).

The knowledge score among lecture attendees significantly improved even after checking for correlated variables, including years of education, current age and duration of opioid use (Repeated measure, Time F=5.3, p = 0.03, Time*Lecture F=7.3, P = 0.009, Time*age P = 0.4, time*duration opiate use P = 0.5, Time*education years P = 0.8, Group-Lecture F=6.3, P=0.01, Group- Education F=6.0, P=0.02, Group-age P=0.2, Group- duration opioid use P = 0.3).

Following the lectures, the level of depression (CES-D score) fell, independently of whether the subject had attended (from 0.8 ± 0.6 to 0.7 ± 0.5) or had not attended the lecture (from 1.0 ± 0.6 to 0.9 ± 0.5) (Repeated measure, Time F=6.7, P = 0.01, Time*Group F=1, P = 0.3, Group F=2.3, P = 0.1). The depression (CES-D) scores before and after the lecture correlated linearly (R=0.78, P < 0.0005), but did not correlate with any other variable.

Questionnaires designed to assess the patient’s knowledge about HCV and depression were completed 12.5±12.5 days (range: 0-79) before and 5.3±8.3 days (range: 0-61) after the lecture, with a mean du-
ration of 17±14 days (range: 2-81) elapsing between the two questionnaires. The time elapsing between questionnaires did not correlate with the depression or knowledge scores (data not shown).

3.3. Attendance of the lectures and referral to the Liver Unit

Of the 80 patients invited, 48 attended the lecture (60%) and 32 (40%) did not (Figure 1). The two groups failed to show differences correlated with any sociodemographic or addiction history indices (data not shown), with depression score (CES-D: 0.8 ± 0.6 vs. 1.0 ± 0.6, respectively, F=1.8, P = 0.2), or with their prior knowledge about HCV (14.9 ± 2.7 vs. 14.5 ± 3.5, respectively, F=0.3 P = 0.6).

Forty-one patients were interested in, and were referred to the Liver Unit (comprising 36/48 [75%] of the lecture attendees as compared with 5/32 [16%] of the non-attendees, P < 0.0005). Those who were referred to the Liver Unit had higher post-lecture knowledge scores than those who were not interested and not referred (18.0 ± 2.4 vs. 16.4 ± 3.3, F=5.8, P = 0.02). Multivariate analysis revealed that attendance at the lecture, but not the post-lecture knowledge score, predicted referral to the Liver Unit: using logistic regression on being referred, the Odds Ratio (OR) for attending the lecture = 13 (95% Confidence Interval (CI) 13.9-44.9 P < 0.0005), while for the knowledge score OR = 1.1 (95% CI 0.9-1.3 P = 0.6).

Only 21 of the 41 referred patients actually presented at the Liver Unit (Figure 2). They had lower depression scores compared with the non-presenters (0.6 ± 0.4 vs. 1.0 ± 0.6, respectively, F=5.7, P = 0.02) and higher knowledge scores before the lecture than the non-presenters (15.8 ± 2.5 vs. 14.2 ± 2.2, respectively, F=4.7, P = 0.04), with no differences in their post-lecture scores. The depression score before the lecture was the only predictor of presentation at the Liver Unit (OR=0.2, 95% CI 0.06-0.9 P = 0.03).

Of the 59 patients that did not present at the Liver Unit (Figure 3) (39 were not referred and 20 were referred, but did not arrive), 37 (62.7%) refused, 8 (13.6%) did not meet inclusion criteria and either did not need treatment or were not eligible (due to negative PCR in 3 cases, psychiatric disorder in 2, pregnancy in 2 and behaviour condition in 1), while 14 (23.7%) were already being treated elsewhere. Of the 39 that were not referred, 12/48 (25%) had attended the lecture and 27/32 (84%) had not. The reasons for non-referral were: refusal (n = 21), no need for therapy (n = 3), not eligible (n = 3), and receiving...
care at other centres (n = 12). Of the 20 who were referred but did not present at the Liver Unit, 16 (80%) refused, 2 were not eligible and 2 were receiving care at other centres.

3.4. Differences between patients already being cared for by a hepatologist and those not being routinely followed up prior to the study

Fourteen patients were already receiving care from a hepatologist elsewhere prior to our study initiation. One-half of them (n = 7) attended the lecture (the rate did not differ from patients who were not routinely being followed up: i.e., 50% vs. 62.1%, P = 0.5). Furthermore, they did not differ in their knowledge about HCV from patients that were not receiving care from a hepatologist (data not shown), but they were less depressed (CES-D) before the lecture (0.7 ± 0.5 vs. 0.9 ± 0.6, P = 0.3), and significantly less depressed following the lecture (0.5 ± 0.4 vs. 0.8 ± 0.5, P = 0.01). Depression decreased at the second evaluation following the lecture, but this was not related to attendance at the lecture, and it differed between those who were being routinely followed up and the others (repeated measured Time F=7.1, P = 0.009, Group-FU F=4, p=0.05, Group-attending lecture p=0.2, Group-interaction P = 0.8).

3.5. Course in the Liver Unit (Figure 2)

Of the total of 21 (60.8%) patients who were referred to and then presented at the Liver Unit, 15 (71.4%) initiated evaluation, 12 (80%) started treatment, and 9 (75%) achieved SVR12.

3.6. Administrative barriers

During the study, 11 patients encountered significant administrative barriers, including: not receiving a reimbursement form, not being able to contact the Liver Unit by phone, and failure in scheduling a doctor’s appointment. Six patients dropped out, resulting in a 54.5% dropout rate (4 were referred to, but then failed to present to the Liver Unit, and 2 dropped out during evaluation at the Liver Unit). Of the 11 patients who experienced administrative barriers, only 5 (41.7%) started treatment (3 achieved SVR, 1 relapsed and 1 stopped due to adverse events).

3.7. Follow-up group

Of the 14 patients who were being followed up elsewhere at the time of study initiation, 1 died from an unknown cause, and 9 were not under treatment when we collected the data (5 were deemed not to be in urgent need of therapy, 3 were apprehensive about

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**Figure 2. Scheme of subgroups who arrived at liver unit**

- Arrived Liver U 21(100%)
  - Initiated evaluation 15(71.4%)
    - Started treatment 12(80%)
      - Success SVR12 9(75.0%)
      - Stopped 2(16.7%)
    - Still evaluating 1(6.7%)
    - Refused 2(9.5%)
      - No need/cannot 4(19.1%)
      - Dropped 2(13.3%)
      - Not respond 1(8.3%)
starting treatment, and one was waiting for interferon-free medications). Of the remaining 4 patients, one was PCR negative, and 3 were co-infected with HIV and being followed up in the infectious disease clinic (one was enrolled and being treated in an anti-HCV clinical trial, but relapsed). Thus, only one (7.1%) of those 14 actually initiated treatment in another centre.

4. Discussion

The results of this study demonstrate that attending one lecture about HCV predicted a better chance of being referred and then starting anti-HCV treatment. Obstacles encountered by the patients that were referred to the Liver Unit were related to administrative barriers, such as getting the appropriate forms or scheduling appointments at the liver clinic. Only one-quarter of the patients who attended the lecture actually initiated anti-HCV treatment (12/48). However, once patients had entered treatment (as mentioned, included PEG-RIBA ± PI, according to the HCV genotype), they achieved a 75% SVR rate. The patients who attended the lecture were more likely to be referred to, then present at the Liver Unit, and, most importantly, be treated there, which suggests that this simple intervention may be highly effective. Our results suggest that a programme that aims to increase knowledge and decrease administrative obstacles among MMT patients may markedly improve their participation in treatment programmes, and ultimately improve their SVR rates.

We cannot, however, entirely exclude the possibility that the successful intervention may be in part due to the way patients are selected. A previous study [10] assessed the efficacy of an explanatory lecture on HCV that was provided to MMT patients by a hepatologist. The authors reported that 50 of 114 HCV seropositive patients attended the initial meeting, 25 (50%) were candidates for treatment, and 20 of the latter were treated. The SVR rate on an intention-to-treat basis was 8/20 (40%). In that study, unlike ours, HCV knowledge, depression scores and their effect on treatment initiation or outcome were not assessed.

We found that a lower CES-D score was a predictor of better compliance with HCV treatment. Similarly, Batki et al. [4] found that depression significantly affected HCV treatment eligibility. The authors showed that, despite psychiatric and substance use comorbidity, most patients were eligible to undergo treatment. Only 15% of their patients were ineligible for HCV treatment: 10% due to failure to complete the evaluation, and 5% due to the severity of the psychiatric illness. Martin et al. [12] reported their results of HCV treatment in active intravenous drug users: pooled intention-to-treat SVR was 45% for genotypes 1 and 4, and 61% for genotypes 2 and 3.

HCV infection carries a high psychological
burden and stigma. A recent study [3], including the interviewing of 31 adults in an integrated HCV treatment programme in an MMT clinic, reported that participants described marked improvements in psychological and behavioural performance over the course of HCV treatment. These included a decrease in internalized stigma and shame related to HCV and addiction, an increase in HCV disclosure and self-care, reduction in substance use, and an increased motivation to help others with HCV.

In our study, 84% of the patients who started treatment against HCV completed the entire treatment. Only 2 patients discontinued treatment because of adverse events, a discontinuation rate similar to that reported in other MMT patient populations. Mauss et al. [14] observed the highest discontinuation rate due to non-compliance or patient request within the first 8 weeks of therapy (22%), while the lowest discontinuation rate was observed in a group of patients without MMT that served as a control group (p = 0.02). However, complete sustained abstinence is only observed in a minority of addicts, and most of them then relapse and once again need opioid maintenance treatment [13].

Our results are in accordance with other reports of HCV treatment outcomes in MMT patients. An excellent outcome and high level of compliance were reported in 19 MMT/buprenorphine patients who were treated for HCV [8]. In order to optimize compliance, the treatment was given in a medication-assisted rehabilitation center, and included psychosocial support. The authors reported a 100% compliance rate, with a 94% SVR rate. The current study supports others in the literature in emphasizing the contribution of improved education and reduced administrative obstacles as tools that enable the achievement of better outcomes in this population.

The effectiveness of an integrated multidisciplinary care model, which included an internist-addiction medicine specialist who was involved in HCV therapy, was assessed in New York [11]. Of 157 patients with detectable HCV RNA, 125 were eligible for referral to the hepatitis clinic, and 76 (61%) were actually referred. Forty-one patients were eligible for treatment, of whom 24 patients entered treatment, 19 completed treatment and 13 (54%) achieved SVR.

Many MMT patients come from low-level socioeconomic backgrounds and are poorly educated. It was therefore challenging to match the level of the lecture with the patients. Indeed, the level of knowledge about HCV before the lecture correlated linearly with the attendees’ years of education, and inversely with their current age and duration of opioid use. These correlations became even stronger in the case of scores for the knowledge about HCV following the lecture. Such findings are to be expected, reflecting the cognitive and learning abilities that are reduced by older age and by longer opioid use, as well as by lower levels of education [20]. Larios et al. [9] reported that two lectures on viral hepatitis are needed to effectively promote knowledge on hepatitis. In the current study, even one lecture was enough to markedly improved knowledge about the virus and its treatments among 48 patients in our MMT clinic. Importantly, we showed that knowledge about HCV improved following the lecture, independently of education, age, and duration of opioid use.

We compared the group of patients that were referred to treatment after attending the lecture with a group of ‘controls’ treated in other centres. Although this was not a randomized controlled trial, that comparison revealed that 12/41 (29.3%) patients were referred to the Liver Unit compared with 1/14 (7.1%) who were receiving care elsewhere.

**Limitations**

One limitation of our study is that the applicability of the results cannot be generalized when implementation involves a regimen that does not involve interferon. It should be remembered that our study was conducted during a transition period in HCV treatment. When the study was conceived and being carried out, HCV therapy for genotype 1 was based on PegIFN-α and ribavirin plus telaprevir or boceprevir; however, several other direct acting antivirals (DAA) have now been approved, both in combination with PegIFN-α and ribavirin (in some parts of the world), or more commonly as IFN-free regimens. Although all-oral regimens have become the new standard of care in chronic HCV management, PegIFN-α and ribavirin-based therapies will remain a potentially important treatment option in such settings as low-income countries or for minorities of patients who have failed DAA-only therapies. Moreover, even in countries where IFN-free regimens are approved and reimbursed, collaborations to reduce bureaucratic barriers and to improve HCV disease awareness in MMT patients are strongly recommended to improve compliance and to increase HCV cure in this group of patients.
5. Conclusions

Our study suggests that a simple intervention such as a lecture and an easy access programme to initiate evaluation for treatment of patients in an MMT clinic may lead to a higher number of patients who initiate treatment for HCV and, eventually, to higher SVR rates. Still, results may not be due to the intervention and might instead be due to patient selection. This possibility is supported by the finding that the fact of having attended the lecture, unlike the post-lecture score, predicted referral to the Liver Unit.

References


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Role of the funding source

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Contributors

All coauthors contributed to the study and manuscript.

Conflict of interest

The authors have no disclosures to report.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

Note

It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author accepted our service.
Methadone maintenance therapy users’ knowledge of, and attitudes towards methadone maintenance therapy: A meta-analysis

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²-Clinical Academic Unit, Newcastle University Medicine Malaysia, Nusajaya, Johor, Malaysia

Summary

Background: Methadone maintenance treatment is effective against opioid dependence. Despite its efficacy, its one-month dropout rate had been reported to be as high as 24%. Studies have associated poor treatment compliance with poor knowledge of and attitude towards treatment. Aim: Our meta-analysis aims to examine the topics of knowledge of and attitude to MMT. Methods: A total of 3,979 participants were recruited from 16 eligible studies, published from inception till August 2015, identified by searching through the PubMed, OVID, EMBASE and EBSCO databases. Results: Our study showed that participants generally had poor knowledge and experience of MMT, and poor attitudes to it. In 7 papers, associated factors of poor attitude to and knowledge of MMT were reported to include: no history of prior or current use of methadone, failure to provide sufficient information, excessive youth, including those who are still too young to qualify when initiating opioid use, depression or stress, admission to detoxification centres, and incarceration. Conclusions: Despite its methodological limitations, this meta-analysis may offer insight to clinicians about poor knowledge, attitudes and perceptions as factors contributing to poor treatment compliance and failure to provide solutions.

Key Words: Methadone; attitude; knowledge; methadone maintenance therapy

1. Introduction

The report published by the United Nations Office on Drugs and Crime (UNODC) in 2014 estimated that 243 million people, equivalent to 5.2% of the world population aged between 15 and 64, had used an illicit drug, with cannabis proving to be the drug most commonly used, followed by opioids. It was also reported that 33 million people used opioids, while 12.7 million people injected drugs [27]. As opioid dependence tends to run a chronic course, the use of opioid agonist maintenance therapy such as methadone maintenance therapy has been recommended and is recognized to be an effective treatment for opioid dependence as a harm reduction programme in many countries [30].

Throughout the years, studies about knowledge of (i.e. the ability to comprehend, acquire, retain and use information [5, 11]), and attitude to (i.e. the interpretation and perception of a topic based on a person’s predisposition towards [5, 11]) opioid agonist maintenance therapy have shown what these are. Studies from China and Taiwan have reported mixed views on MMT, and even its rejection by a fraction of opioid-dependent patients. Among the misconceptions reported were “Methadone is dangerous and addictive”, and “Methadone is hard to withdraw and causes poor health” [15, 33]. These negative attitudes taken up by methadone users towards MMT may affect their progression and motivation in an MMT programme. As a result, despite the support given by many countries to this harm reduction programme, the effort to scale up MMT programmes remains a challenge.

The attitudes of methadone users towards MMT can be associated with several factors. Firstly, the knowledge of methadone users towards MMT needs to be studied. Information received by methadone us-
ers may affect their favourable/unfavourable attitude to MMT and so influence their performance in any MMT programme. Previous studies found that many substance users have received false information about methadone. In one of the studies that was done in the UK to study the attitudes of drug users towards buprenorphine and methadone, participants reported that buprenorphine acts as a better opioid to replace heroin than methadone, by claiming buprenorphine is more effective in reducing cravings for heroin [21]. Past studies, however, have demonstrated that this is not true [22].

Despite the importance of understanding the attitudes of methadone users towards MMT, and their knowledge of it, there is a lack of the quantifiable data required to examine the knowledge of and attitude towards MMT in this group of patients. The aim of this systematic review and meta-analysis must therefore take the form of examining the knowledge of and attitudes towards methadone by systematically review-
ing and collating the findings of the primary literature on this topic.

2. Methods

2.1. Study selection

This study was designed in accordance with PRISMA guidelines. We included all studies in the literature written in English in the period 2008 to January 2016. The primary outcome was providing an overview of the knowledge of, and attitudes taken towards methadone maintenance therapy. The main secondary outcome was a review of the factors that contribute to influencing methadone users’ knowledge of and attitudes towards MMT. Only studies which met the following criteria were included: 1) Participants had to be at least 18 years old; 2) There had to be previously or currently involved in methadone therapy; 3) Availability in the text of quantita-

Table 1: The quality, designs and aims of 16 eligible studies

<table>
<thead>
<tr>
<th>Study</th>
<th>NOS</th>
<th>D</th>
<th>Ethnicity</th>
<th>Eligibility Criteria</th>
<th>Methadone duration</th>
<th>Setting</th>
<th>Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Gryczynski et al., 2013 USA</td>
<td>5</td>
<td>0</td>
<td>3 8 1Y African American 75 Others 5</td>
<td>Previous MMT/ BMT/out of treatment Individuals starting buprenorphine treatment</td>
<td>NR</td>
<td>BMT outpatients</td>
<td>Conveni-ent</td>
</tr>
<tr>
<td>2-Marchand et al., 2015 Canada</td>
<td>3</td>
<td>2</td>
<td>2 7 NR Non-aboriginal 70% Aboriginal 30%</td>
<td>At least 5 years of illicit opioid use, regular use of illicit opioids during the prior 6 months</td>
<td>Median=36 months</td>
<td>MMT outpa- tients</td>
<td>Snowball</td>
</tr>
<tr>
<td>3-Liu et al., 2013 China</td>
<td>1</td>
<td>0</td>
<td>2 3 NR Han Chinese 418 Minority Chinese 6</td>
<td>Receiving MMT for at least 3 months continu-ously prior to participa- tion.</td>
<td>At least 3 months</td>
<td>MMT/ compuls- ory detoxification inpatients and outpa- tients</td>
<td>Conveni-ent</td>
</tr>
<tr>
<td>4-Madden et al., 2008</td>
<td>4</td>
<td>0</td>
<td>2 6 NR Australian 371 Others 61</td>
<td>Receiving supervised dose at a stratified sample of 9 public opioid treatment clinics</td>
<td>Any dura-tion</td>
<td>BMT/MMT outpa- tients</td>
<td>Conveni-ent</td>
</tr>
<tr>
<td>5-Pinto et al., 2008 UK</td>
<td>1</td>
<td>0</td>
<td>2 3 NR NR</td>
<td>Well adult consented patients on MMT/BMT</td>
<td>NR</td>
<td>MMT/BMT outpa- tients</td>
<td>Conveni-ent</td>
</tr>
<tr>
<td>6-Rieckmann et al., 2010 USA</td>
<td>4</td>
<td>2</td>
<td>2 8 NR African Americans 9.6% Hispanics 5% Multi racial 8% Others 77.4%</td>
<td>Met admissions criteria for level of care where they were recruited.</td>
<td>NR</td>
<td>Any OAT, in- patients and outpa- tients</td>
<td>Conveni-ent</td>
</tr>
<tr>
<td>7-Vijay et al., 2015 Malaysia</td>
<td>4</td>
<td>2</td>
<td>3 9 NR Malay 416 Indian 31 Chinese 12</td>
<td>Self reported drug injection in prior 30 days and willing to undergo HIV testing and urine toxicology screening</td>
<td>Any dura-tion</td>
<td>BMT/MMT outpa- tients, patients for HIV testing</td>
<td>Snowball</td>
</tr>
<tr>
<td>8-Xu et al., 2012 China</td>
<td>4</td>
<td>0</td>
<td>1 5 1Y NR</td>
<td>Active local heroin user with no prior history of MMT treatment</td>
<td>New pa- tients, not taken any dose</td>
<td>MMT outpa- tients</td>
<td>Conveni-ent</td>
</tr>
<tr>
<td>9-Yen et al., 2011 Taiwan</td>
<td>5</td>
<td>2</td>
<td>2 9 1Y NR</td>
<td>HIV positive IVDU inmates</td>
<td>NR</td>
<td>HIV positive inma tes</td>
<td>Conveni-ent</td>
</tr>
</tbody>
</table>

NOS= Newcastle-Ottawa Scoring, S= selection of study group, C= comparability of the group, O= ascertainment of outcome of interest in studies, T= total score of NOS, D= duration, Y=year, M=month, NR= non report, MMT= methadone maintenance therapy, BMT= Buprenorphine maintenance therapy, NR= non report, HIV= human immunodeficiency virus, IVDU= intravenous drug user.
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<th>Eligibility Criteria</th>
<th>Methadone duration</th>
<th>Setting</th>
<th>Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Zaller et al., 2009 USA</td>
<td>4</td>
<td>0</td>
<td>2 6 1Y 4M</td>
<td>Hispanic 39 Black 14</td>
<td>Not taken any dose</td>
<td>IVDU not on MMT</td>
<td>Convenient</td>
</tr>
<tr>
<td>11-Alves et al., 2011 UK</td>
<td>4</td>
<td>1</td>
<td>1 6 1M</td>
<td>White 67.8% Non white 32.2%</td>
<td>Consented adults receiving MMT/BMT</td>
<td>Any duration</td>
<td>MMT/BMT outpatients</td>
</tr>
<tr>
<td>12-Stancliff et al., 2002 USA</td>
<td>3</td>
<td>2</td>
<td>1 6 2D</td>
<td>American African 37% White 14% Latino 43% Other/un-known 6%</td>
<td>All willing patients waiting in line at each nursing station for their methadone doses.</td>
<td>Mean 7 years, range 1 week to 30 years</td>
<td>MMT outpatients</td>
</tr>
<tr>
<td>13-Winstock et al., 2008 Australia</td>
<td>4</td>
<td>1 3</td>
<td>8 1Y</td>
<td>Australian born 87% Non-Australian born 13%</td>
<td>All consented clients receiving supervised methadone or buprenorphine dose at participating clinic or pharmacies.</td>
<td>Any duration</td>
<td>MMT outpatients</td>
</tr>
<tr>
<td>14-Kelly et al., 2012 USA</td>
<td>5</td>
<td>1</td>
<td>2 8 2Y</td>
<td>African American 83% White 16.1% Hispanic 0.4% Others 0.5%</td>
<td>Adult participants with at least 1 year history of opioid use.</td>
<td>NR</td>
<td>BMT/MMT/out-of-treatment patients</td>
</tr>
<tr>
<td>15-Schwartz et al., 2008</td>
<td>5</td>
<td>1</td>
<td>2 8 NR</td>
<td>American African 73.8% Caucasian 24.6% Others 1.5%</td>
<td>Consented adults that met requirements for methadone treatment.</td>
<td>NR</td>
<td>MMT outpatients/out of treatment participants</td>
</tr>
<tr>
<td>16-Bachired-dy et al., 2011</td>
<td>3</td>
<td>2</td>
<td>2 7 1M</td>
<td>Malay 96.1% Others 3.9%</td>
<td>HIV positive IVDU inmates</td>
<td>NR</td>
<td>HIV positive inmates</td>
</tr>
</tbody>
</table>

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tive data.

2.2. *Data sources and data extraction*

The authors conducted a systematic search on the PubMed, EMBASE, EBSCO and Ovid databases to identify potentially appropriate papers using the following MeSH items: “opioid replacement therapy” or “medical assisted therapy” or “opioid agonist therapy” or “methadone maintenance therapy”; and “knowledge” or “attitude” or “perception” or “belief”. The bibliographies of all the studies selected were checked, with the aim of identifying additional studies worthy of inclusion.

For papers that were not otherwise available or that provided inadequate data, we contacted the authors via email to obtain the full paper and/or more detailed data from them. The titles and abstracts obtained through electronic search were the first elements to be screened by two independent authors, followed by the full-text articles. To keep this review as precise as possible, we excluded any study that involved patients who had used methadone to alleviate non-malignant or malignant pain, and studies that involved injectable methadone only. We also excluded case reports, systemic reviews, case series, and duplicate publications (i.e., 2 or more studies investigating the same samples). We allowed all methods of measuring the attitude to, and knowledge of MMT in this group of patients.

2.3. *Quality assessment*

Each of the two authors independently assessed
Table 2. Factors that influenced the methadone users’ knowledge and attitude towards MMT

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior/current use of methadone</th>
<th>Female</th>
<th>Information provision</th>
<th>Young age</th>
<th>Young age initiating heroin use</th>
<th>Depression/Stress</th>
<th>BMT</th>
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+ = Positive correlation, – = negative correlation, O = no correlation

the quality of the methodology and reporting of the studies using Newcastle-Ottawa Scoring (NOS) Scale citation. Any discrepancies were sorted out by the third reviewers. The NOS scale was developed to assess the quality of non-randomized, cross-sectional studies to strengthen the interpretation of our meta-analytical results. That scale uses a ‘star system’ that judges those studies from three broad perspectives: the selection of a study group (S), the comparability of that group (C) and how best to ascertain the outcome of interest in studies (O). The scale itself has a total score of 10 (1 star carries a score of 1 point).

2.4. Data synthesis

Qualitative: All abstracted information was tabulated. A qualitative meta-analysis was then carried out by summarizing, comparing, and contrasting the abstracted data.

Quantitative: All data analyses were performed using StatsDirect, version 2.7.9 (StatsDirect Ltd, UK). The presence of heterogeneity between the trials was tested using the I-squared (I²) statistic. An I² value of over 75% indicates significant heterogeneity [8, 9]. We gathered individual study data through random effects (DerSimonian–Laird) proportion meta-analysis if I² was significant. Publication bias was assessed by using a random effects meta-analysis, which, in its turn, was carried out using a Begg-Mazumdar and Egger test.

3. Results

The initial search strategy identified 1,383 titles: 428 from PubMed, 107 from Ovid, 374 from Embase, 474 from PsycArticles and EBSCO (Figure 1). Title screening and elimination of duplicate publications yielded 154 publications from PubMed, 76 from
We then excluded 516 publications after reviewing the abstract, and obtained the full text of the remaining 19 studies, of which 16 were eligible for inclusion in this review. The method of data extraction is shown in Figure 1, which is in accordance with the Quality of Reporting of Meta-Analyses Guidelines.

The 16 eligible studies included 6,373 eligible subjects, of which 3,979 consented and participated. The mean age of the subjects was reported in 12 papers as being within the range of 33-45.2 years old. Methadone therapy duration was only described in 9 papers; in those it was reported as ranging between 3 months and 30 years. A majority of these studies showed a methadone treatment duration of at least 6 months.

### Table 3: The knowledge and attitude towards methadone maintenance therapy.

<table>
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<th>S</th>
<th>EP</th>
<th>AS</th>
<th>Gender</th>
<th>Age (m)</th>
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<th>Knowledge towards MMT</th>
<th>Attitude towards MMT</th>
<th>Service mode</th>
<th>Service provider</th>
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<td></td>
<td>Negative 95%(n=76) said “Methadone is bad for you physically.” 65%(n=52) said for “You have to stay on methadone too long.” 91.3%(n=73) said “The withdrawal from methadone is worse than buprenorphine.”</td>
<td>Negative 75%(n=60) stated, “You don’t like how methadone makes you feel.” 53.8%(n=43) stated, “People on methadone aren’t really clean.” 43.8%(n=35) stated, “Other people would not want you to take methadone.” 46%(n=37) stated “You think methadone treatment is a last resort for people who can’t stop using by any other means.”</td>
<td>Positive 91.3%(n=73) scored not important for “The rules at methadone programs are too strict.” 88.8%(n=71) scored not important for “Methadone treatment is too expensive.”</td>
<td>Negative 41.3% (n=33) scored important for “People at methadone clinic aren’t serious about recovery.”</td>
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<td>1</td>
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<td>160</td>
<td>329*</td>
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<td>74</td>
<td>44.9</td>
<td>SIQ</td>
<td>Positive 18.2%(n=60) stated the treatment reduces daily stressors and criminal involvement and improves financial situation. 6.1%(n=20) stated methadone helps to gain control over illicit drug use. Negative 29.6%(n=118) stated MMT is associated with adverse mental and physical health and reduces overall functioning.</td>
<td>Positive 12.5%(n=41) stated treatment is accessible, convenient and delivered at no cost. Negative 16.1%(n=64) stated the barriers to treatment adherence include frequency of physician and pharmacy visits, wait times and general time demands of treatment. Negative 14.6(n=58) stated negative interaction with health care staff resulting from perceived trust and lack of interaction. 15.8%(n=63) stated the feeling of lack of autonomy in treatment decisions.</td>
<td>Positive 34.7%(n=114) stated MMT reduces withdrawal symptoms</td>
</tr>
</tbody>
</table>

S=Study, EP= Eligible participants, AS= Analytical sample, m=mean, I= Instruments, MMT= methadone maintenance therapy, SIQ= Self invented questionnaire, * positive references and negative references, HCV/HIV/AIDS= hepatitis C/ human immune deficiency virus/acquired immune deficiency syndrome, NR = not reported, VAS= visual analogue score, CAMP= Client Attitudes Towards Methadone Program scale, IDU= intravenous drug users, ATMS= Attitude towards methadone scale, SE= Standard error
of, and attitude towards methadone maintenance, 3 papers adapted or used the work of Schwartz et al., [25], 2 papers adapted or used the work of Winstock et al., and 2 papers used Stancliff et al., [26], questionnaire. The treatment perception questionnaire, Medication opinion survey and Client’s attitude towards methadone programme scale were each used by 1 paper.

3.1. Description of selected study populations

The designs and aims of all eligible studies are listed in Table 1. Most previous studies were cross-sectional and had knowledge of, and attitudes towards MMT as their outcome. Most of those studies were conducted in outpatient clinics or methadone maintenance therapy clinics. Only 7 of these studies were compared with a buprenorphine group/compulsory detoxification group/out of treatment group. Seven of the studies were conducted in North America, while another five studies involved patients from Asia (i.e., Malaysia, China, Taiwan). Australia and UK contributed two studies each.

The 10 associated clinical factors were investigated in the 16 studies; they included age, gender, information provision, age when initiating heroin use, depression/stress, involvement in Buprenorphine Maintenance Therapy, admission to a compulsory detox centre, any recourse to the sharing of needles/syringes, and ethnicity (Table 2).

3.2. The knowledge of methadone users

Less than half of the participants agreed that methadone can reduce HIV/HCV risk (Pooled Prevalence [PP] = 44%, 95% Confidence Interval (CI) = 0.40-0.49) [15, 24, 34] or can reduce crime (PP=26%, 95% CI=0.04-0.58) [16, 26, 28]. On the other hand, more than half agreed that methadone has worse withdrawal compared to opioids.

Table 3: The knowledge and attitude towards methadone maintenance therapy.

<table>
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<td>M</td>
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<td>SIQ</td>
<td>Positive 62.5% (n=70) agreed that methadone reduces illicit drug use.</td>
<td>Positive 80.2% (n=90) agreed that methadone enables them to live a normal life.</td>
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<td>3</td>
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<td>18</td>
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<td>Positive 62.2% (n=69) agreed that methadone prevents HCV/HIV/AIDS</td>
<td>Positive 56.8% (n=63) agreed that methadone is addictive.</td>
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<td>Negative 49.1% (n=55) agreed that methadone is bad for health</td>
<td>Negative 54.5% (n=61) agreed that methadone has worse withdrawal compared to opioids.</td>
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<td>19.6% (n=22) agreed that non-MMT patients are looking them down.</td>
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<td>28.8% (n=32) agreed that they feel shameful about using methadone.</td>
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</tbody>
</table>

S=Study, EP= Eligible participants, AS= Analytical sample, m=mean, I= Instruments, MMT= methadone maintenance therapy, SIQ= Self invented questionnaire, * positive references and negative references, HCV/HIV/AIDS= hepatitis C/ human immune deficiency virus/acquired immune deficiency syndrome, NR = not reported, VAS= visual analogue score, CAMP= Client Attitudes Towards Methadone Program scale, IDU= intravenous drug users, ATMS= Attitude towards methadone scale, SE= Standard error
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<td>432</td>
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<td>266</td>
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<td>35.7</td>
<td>Negative 15% (n=64) reported physical health as best thing regarding treatment.</td>
<td>Positive 12% (n=52) reported no criminal activity as the best thing regarding treatment.</td>
<td>Negative 54% (n=233) agreed that they had not liked some of the rules and regulations.</td>
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<td>14% (n=60) report getting off of treatment as the worst thing regarding treatment.</td>
<td>27% (n=117) reported stability as the best thing regarding treatment.</td>
<td>32% (n=138) agreed frequency of clinic attendance as worst thing regarding treatment.</td>
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<td>31% (n=134) reported no heroin use as best thing regarding treatment.</td>
<td>Negative 15% (n=65) reported being ‘stuck’ on treatment as worst thing regarding treatment.</td>
<td>15% (n=65) reported inflexibility with travel, employment and family as worst thing regarding treatment.</td>
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</table>

|   |    |    |        |        |    | Positive 12% (n=52) reported no criminal activity as the best thing regarding treatment. | Negative 54% (n=233) agreed that they had not liked some of the rules and regulations. | Positive 63% (n=272) agreed that there is a staff member available when client wants to talk. |
|   |    |    |        |        |    | 14% (n=60) report getting off of treatment as the worst thing regarding treatment. | 27% (n=117) reported stability as the best thing regarding treatment. | 32% (n=138) agreed frequency of clinic attendance as worst thing regarding treatment. | 69% (n=298) agreed that the prescriber listens to the clients’ view on treatment. |
|   |    |    |        |        |    | 31% (n=134) reported no heroin use as best thing regarding treatment. | Negative 15% (n=65) reported being ‘stuck’ on treatment as worst thing regarding treatment. | 15% (n=65) reported inflexibility with travel, employment and family as worst thing regarding treatment. | Negative 55% (n=238) agreed that staff have not always understood the kind of help client wants. |

3.3. The attitude of methadone users

In general, only 53% of participants felt that methadone had in some way changed them to being able to live a better life (PP=53%, 95% CI=0.21-0.83) [15, 16, 24, 26], and less than half of participants agreed that methadone can control their use of opioids (PP=43%, 95% CI=0.26-0.60) [15, 16, 26, 28, 35], while only 39% of participants felt ashamed when using methadone (PP=39%, 95% CI=0.23-0.57) [15, 24, 34]; a majority felt that people should leave their methadone therapy as soon as possible (PP=57%, 95% CI=0.36-0.76) [24, 26, 28, 31, 34], and nearly half viewed methadone maintenance as a form of addiction (PP=49%, 95% CI=0.21-0.77) [7, 15, 16, 26, 28, 34]. 42% of participants felt they had been discriminated against or looked down on due to their use of methadone (PP=42%, 95% CI=0.25-0.59) [7, 15, 24, 28, 34] (Table 3).

3.4. Experiences of methadone users

MMT was viewed by over half of the participants as being inflexible to the extent of making their lives difficult (PP=51%, 95% CI=0.15-0.86) [16, 34]. Other people complained about this and the strict regulations enforced at the methadone clinic (PP=29%, 95% CI=4.1-0.77) [7, 16], adding that methadone is expensive (PP=41%, 95% CI=0.15-0.70) [7, 28, 34]. 61% of participants preferred to have their methadone prescribed at a regular doctor’s office (95% CI=0.56-0.66) [24, 34].
A. Yee et al.: Methadone maintenance therapy users’ knowledge of, and attitudes towards methadone maintenance therapy: A meta-analysis

Ten maintenance therapy possess an unsatisfactory amount of knowledge about MMT compounded by a negative attitude towards it. Knowledge has been defined as the ability to comprehend, acquire, retain and use information [5]. In our context, knowledge about methadone means an understanding of methadone as an effective treatment and its health benefits [20]. Our study shows that more than half of these MMT patients have only a poor knowledge of methadone. Misconceptions include the belief that methadone is an ineffective treatment for opioid dependence, that methadone has negative health implications, and that it is unable to prevent diseases spread by intravenous drug use.

The poor knowledge referred to above may be

Regarding clinical staff, only less than a quarter of these MMT participants thought that clinical staffs were unfriendly or unhelpful. (PP=18%, 95% CI=0.07-0.31). However, more than half of the participants felt that the staff did not understand their need (PP= 57%, 95% CI=0.50-0.65). [16, 34] (Table 3).

4. Discussion

This is the first meta-analysis to describe the knowledge, attitudes and experiences of methadone maintenance therapy (MMT) patients, and the factors associated with them. The results of this meta-analysis go to show that participants in methadone maintenance therapy possess an unsatisfactory amount of knowledge about MMT compounded by a negative attitude towards it.

Knowledge has been defined as the ability to comprehend, acquire, retain and use information [5]. In our context, knowledge about methadone means an understanding of methadone as an effective treatment and its health benefits [20]. Our study shows that more than half of these MMT patients have only a poor knowledge of methadone. Misconceptions include the belief that methadone is an ineffective treatment for opioid dependence, that methadone has negative health implications, and that it is unable to prevent diseases spread by intravenous drug use.

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</table>

Mean score attitudes of methadone clients towards methadone=6.98 Mean score of perceived social norms of methadone clients towards methadone=2.37 Mean score behavioural intentions of methadone clients towards methadone=2.76

S=Study, EP= Eligible participants, AS= Analytical sample, m=mean, I= Instruments, MMT= methadone maintenance therapy, SIQ= Self invented questionnaire, * positive references and negative references, HCV/HIV/AIDS= hepatitis C/ human immune deficiency virus/ acquired immune deficiency syndrome, NR = not reported, VAS= visual analogue score, CAMP= Client Attitudes Towards Methadone Program scale, IDU= intravenous drug users, ATMS= Attitude towards methadone scale, SE= Standard error
due to a variety of reasons. Firstly, previous studies had shown inadequate provision of information on methadone [1] by healthcare providers. Secondly, several studies have shown that some healthcare professionals and staff members at detention centres or in incarceration settings have a poor knowledge of methadone and adopt a negative attitude towards MMT [2-4, 19]. It is clear that staffs that are poorly trained are unable to correct misconceptions about methadone or perform effective counselling. Thirdly, Yen at al., and Vijay et al., had reported an association of young MMT patients and participants who became involved in opioid use when still very young, at a time when they had only a poor knowledge of and attitude towards methadone [28, 33]. This may be related to their early dropout from the educational system and a subsequent poor understanding of MMT due to their low educational status.

Attitude is the interpretation and perception of a topic based on a person’s predispositions [11]. In our context, negative attitudes are perceptions that distance the patient from MMT. Although a majority (53%) of patients agreed about the positive life changes methadone had brought them [15, 16, 26], a striking 57% (95% CI=0.36-0.76) had been pressured to leave MMT [24, 26, 28, 31, 34]. Other negative attitudes included feelings of guilt and shame while using methadone [15, 24, 34], and the mindset that MMT is temporary, so that participants should be taken off methadone as soon as possible [24, 26, 28, 31, 34].

This ambivalent attitude towards MMT may

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**Table 3: The knowledge and attitude towards methadone maintenance therapy.**

<table>
<thead>
<tr>
<th>S</th>
<th>EP</th>
<th>AS</th>
<th>Gender</th>
<th>Age (m)</th>
<th>I</th>
<th>Knowledge towards MMT</th>
<th>Attitude towards MMT</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td></td>
<td>Positive 63% (n=289) agreed that MMT is the best way to treat opioid addiction</td>
<td>Positive 62% (n=285) agreed that methadone keeps client from injecting</td>
</tr>
<tr>
<td>7</td>
<td>460</td>
<td>460</td>
<td>443</td>
<td>17</td>
<td>38.8</td>
<td>Negative 32% (n=147) agreed that MMT is bad for a person’s health</td>
<td>Negative 47% (n=216) agreed that methadone treatment is expensive</td>
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<td></td>
<td>25% (n=115) agreed that people look down on those on methadone.</td>
<td>25% (n=115) agreed that people look down on those on methadone.</td>
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<td></td>
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<td></td>
<td>30% (n=138) agreed that methadone encourages people to use more of other drugs.</td>
<td>30% (n=138) agreed that methadone encourages people to use more of other drugs.</td>
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<td></td>
<td>49% (n=225) agreed that people should try to get off therapy as soon as they can.</td>
<td>49% (n=225) agreed that people should try to get off therapy as soon as they can.</td>
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<td></td>
<td>79% (n=363) agreed that methadone only replaces one addiction with another</td>
<td>79% (n=363) agreed that methadone only replaces one addiction with another</td>
</tr>
</tbody>
</table>

S=Study, EP= Eligible participants, AS= Analytical sample, m=mean, I= Instruments, MMT= methadone maintenance therapy, SIQ= Self invented questionnaire, * positive references and negative references, HCV/HIV/AIDS= hepatitis C/ human immune deficiency virus/ acquired immune deficiency syndrome, NR = not reported, VAS= visual analogue score, CAMP= Client Attitudes Towards Methadone Program scale, IDU= intravenous drug users, ATMS= Attitude towards methadone scale, SE= Standard error
Table 3: The knowledge and attitude towards methadone maintenance therapy.

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<tr>
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<th>EP</th>
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<th>Gender Age (m)</th>
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<th>Knowledge towards MMT</th>
<th>Attitude towards MMT</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>SIQ</td>
<td></td>
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<tr>
<td>8</td>
<td>307</td>
<td>300</td>
<td>277</td>
<td>23</td>
<td>NR</td>
<td>Negative 92.3% (n=277) believed that MMT is intended primarily for detoxification. 64.2% (n=193) believed that one should be completely detoxified and quit using methadone after using it for 2-3 months. 77.9% (n=234) believed that MMT is not a long term/lifetime treatment. 84.3% (n=253) believed that one should try to reduce treatment dosage, as methadone is harmful to one’s health.</td>
</tr>
<tr>
<td>9</td>
<td>328</td>
<td>315</td>
<td>219</td>
<td>96</td>
<td>35.2</td>
<td>CAMP</td>
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<tr>
<td>10</td>
<td>53</td>
<td>53</td>
<td>42</td>
<td>11</td>
<td>40</td>
<td>SIQ adapted from Stancliff et al.</td>
</tr>
</tbody>
</table>

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be caused by poor knowledge towards methadone [7, 15-17, 24, 28, 31, 34, 35] and poor experiences in the MMT clinic [7, 16, 34]. In addition, negative attitudes towards
### Table 3: The knowledge and attitude towards methadone maintenance therapy.

<table>
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<tr>
<th>S</th>
<th>EP</th>
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<th>Gender</th>
<th>Age (m)</th>
<th>I</th>
<th>Knowledge towards MMT</th>
<th>Attitude towards</th>
<th>Service mode</th>
<th>Service provider</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M</td>
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<td></td>
<td>Mean score was 14.74 (SD=4.7, range 2-25)</td>
<td>Positive</td>
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<tr>
<td>11</td>
<td>154</td>
<td>118</td>
<td>96</td>
<td>22</td>
<td>NR</td>
<td>SIQ adapted from Win-</td>
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<td>Positive</td>
<td>60% (n=189) agreed</td>
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<td></td>
<td></td>
<td>“Since I have been on methadone I am more careful about using condoms and choosing whom to have sex with”</td>
<td>-</td>
<td>58% (n=183) disagreed</td>
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<td></td>
<td></td>
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<td></td>
<td>Negative 47% (n=148) agreed, “Methadone is bad for your health.”</td>
<td>Positive</td>
<td>79% (n=249) disagreed</td>
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<td></td>
<td>39% (n=123) agreed on statement “Higher doses of methadone are less healthy than lower doses.”</td>
<td>-</td>
<td>80% (n=252) agreed</td>
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<td></td>
<td>71% (n=224) agreed on statement “Methadone gets in your bones.”</td>
<td>Positive</td>
<td>54% (n=170) agreed</td>
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<td></td>
<td>60% (n=189) agreed and not sure that “Methadone damages the immune system.”</td>
<td>-</td>
<td>53% (n=167) agreed</td>
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<td>43% (n=135) disagreed that methadone helps people be more careful about using a clean syringe if they still shoot up.</td>
<td>Negative</td>
<td>-</td>
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<td></td>
<td>61% (n=192) disagreed that “Being on methadone helps drug users avoid getting HIV.”</td>
<td>Negative</td>
<td>68% (n=214) agreed</td>
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<tr>
<td></td>
<td>800</td>
<td>315</td>
<td>176</td>
<td>139</td>
<td>42</td>
<td>SIQ 16 item</td>
<td>Positive</td>
<td>55% (n=173) agreed</td>
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<td></td>
<td></td>
<td>“People would be helped if methadone were offered in regular doctors’ offices.”</td>
<td>Positive</td>
<td>61% (n=192) agreed</td>
<td></td>
</tr>
</tbody>
</table>

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methadone are commonly encountered in opioid dependence treatment providers [2-4, 18]. Stancliff et al., reported that MMT participants are often not allowed to talk in many 12-step settings, and that they are denied life-saving procedures such as liver transplants [26]. Indeed, several studies suggest that many healthcare providers still believe in abstinence-based programmes in preference to MMT [2-4]. When the staff at methadone clinics are sceptical, they not only fail to educate patients because of their biased attitudes, they also provide unsatisfactory services.

Several studies have identified factors associated with poor knowledge of, and attitudes to MMT. These include: being male [1, 24], no history of prior or current use of methadone [1, 15, 23, 26, 28, 31, 33], lack of information made available to patients [1], low age [28, 31, 33], low age at initiation of heroin use [31, 33], depression or stress [28, 31, 33], incarceration or admission to detoxification centres [15, 28].

There have been detailed reports that male patients are less likely to express interest in seeking counselling or help [6]. This natural repulsion for making the effort needed to request help predisposes male subjects to refrain from obtaining information about MMT, hence their poor knowledge and attitudes. Previous research had similarly found that an early onset of substance use is associated with low percentages of individuals seeking treatment [12].

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<td>MMT</td>
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<td>Positive 86.9%(n=688) disagreed that “mixing alcohol and benzodiazepines with methadone does not increase the risk of overdose”</td>
<td>-</td>
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<td></td>
<td></td>
<td>Negative 74.5%(n=590) disagreed that people in MMT are protected against opioid overdose.</td>
<td>-</td>
</tr>
</tbody>
</table>

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This is thought to be due to the adverse social and mental consequences of substance use, including a low level of educational attainment, teen childbearing, economic adversity and psychopathology, all of which act as barriers to MMT [13, 32]. Depression may cause poor attitudes towards MMT in several ways. Firstly, depression is linked with poor self-esteem and a higher influence exerted by peers, including peers hostile to MMT [10]. Secondly, depressed intravenous drug users commonly self-medicate against insomnia and depressed mood by taking substances, and they are usually not keen to change [14]. Thirdly, our study had shown that negative affect may reduce drug-takers’ commitment to proactive and reactive cognitive control, so leaving them unmotivated to solve their problems [29]. Liu et al., reported that a percentage as high as 90% of individuals held in drug detention centres in Ningbo, China, did not list MMT as their preferred method of treatment [15]. This may be due to their lack of information about, and a preference for abstinence rather than MMT [3, 4].

Past studies had shown that a good knowledge
of, and positive attitude towards treatment are associated with better treatment readiness, compliance and outcomes [16, 20, 21, 25, 35]. There is therefore a need to develop standard tools to ensure that information on MMT has been understood by patients. It is also important to develop specific protocols when health staff deliver information to MMT participants [35]. Since misconceptions regarding methadone are a common finding in out-of-treatment patients, interventions should target prospective MMT clients and opioid users in detention centers and prison settings [31]. Training of MMT staff is of the utmost importance in permitting correct information and concepts to be delivered to MMT group members.

Limitations

This study is not without its limitations. First, only contributions to the literature written in English were being reviewed. Next, most of the studies reviewed use self-invented questionnaires that had not been validated. Most papers did not compare different groups of MMT participants, so making any sub-analysis of data impossible. Lastly, only 2 studies discussed associated factors of knowledge about, or attitude levels towards MMT, with each paper dedicated to different factors, so raising the chances of reporting a biased result.

5. Conclusions

This study suggests that poor knowledge of, and attitudes towards MMT as found in MMT patients remain a challenge, and they may well contribute to the high dropout rates recorded for MMT programmes, despite these programmes’ proven efficacy and health benefits. Interventions should be taken to improve knowledge of, and attitudes towards MMT, not only in patients that are actually receiving MMT, but also in prospective out-of-treatment clients and those in detention centres and incarcерation settings.

References

Heroin Addiction and Related Clinical Problems 19(3): 21-36

The Role of Gender in Factors Associated With Addiction Treatment Satisfaction Among Long-Term Opioid Users. J Addict Med. 9(5): 391.


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Contributors
AY and JTT designed the review protocol and extraction forms in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. AY and JTT conducted a search of published English-language literature by independently extracting the primary data, which were then reviewed systematically. AT and HMY independently assessed the quality of the studies. Disagreements were discussed and resolved by AY and LHS, who acted as mediators.

Conflict of interest
Authors declared no conflict of interest.

Ethics
This study does not require ethics committee approval.

Note
It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author accepted our service.
Drug addiction and emotional dysregulation in young adults

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2-VP Renata Therapeutic Community, Venice, Italy, EU
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4-La Sapienza University of Rome, Department of Clinical and Dynamic Psychology, Italy, EU
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Summary

Background: It is widely acknowledged that drug addiction is characterized by emotional dysregulation. Relatively few studies in this field, however, have focused on early adulthood. Aim: The present study aims to assess emotional functioning in young adults (aged 18-24) with drug addiction who have already been admitted to residential treatment. Methods: A group of young drug addicts admitted to residential treatment (N=41) was compared with a group of young adults without Substance Use Disorder (N=27). A series of psychological self-report questionnaires on emotional functioning, Toronto Alexithymia Scale-20 item, Sensation Seeking Scale–VI, Emotional Quotient Inventory and Observer Alexithymia Scale were administered. Descriptive and nonparametric analyses (Pearson’s chi square test, Mann-Whitney U test, and McNemar test) were performed. Results: High rates of alexithymia emerged from the administration of the observer scale, in contradiction with the self-report evaluation; also, past experiences related to sensation seeking and inadequate emotional intelligence abilities were identified as characteristics of this clinical group. Conclusions: Our results suggest that drug dependence in young adults is characterized by difficulties in emotional regulation, indicating the importance of specific and new treatment methodologies.

Key Words: Youths; drug addiction; alexithymia; emotional dysregulation

1. Introduction

Adolescence implies significant neurodevelopmental changes, with remarkable functional and structural alterations that involve cortical and subcortical brain areas. In particular, the process known as ‘frontalization’ takes place, meaning the development of the pre-frontal cortex and the consequential maturation of higher cognitive abilities and reinforcement of cognitive control over the emotional and behavioural responses initiated by the limbic structures [71, 81]. The “dual system” model highlights a substantial difference in the developmental trajectories of these two neurobiological systems: the socioemotional system, localized in the limbic and paralimbic areas, develops more rapidly than the cognitive control system, which fully develops only in early adulthood [89]. Given this asynchrony, adolescents face stronger bottom-up reward-related drives but, at the same time, they cannot rely on adequate regulation abilities, resulting in a vulnerability to impulsive and risk-taking behaviours, often in terms of experimenting and using substances, whether licit or illicit [85]. As a matter of fact, nowadays, Substance Use Disorders (SUD; [3]) in young people are a matter of increasing concern. Among patients undergoing drug addiction treatment, there is an increasing percentage of youths aged 18-24: one estimate published as recently as 2013 puts the percentage of addicted patients younger than 25 years at 27% [32]. Furthermore, the recent phenomenon of drug misuse shows peculiar characteristics of heightened risk, such as the widespread use of amphetamine-type stimulants and new psychoactive drugs [101] and the form of multi-
ple consumption called polydrug use [31].

1.1. Emotional dysregulation in drug addiction

Emotional regulation is a multidimensional construct, encompassing different abilities and processes that share the goal of maintaining and/or modifying the current or expected affective state, as regards its intensity, quality and duration. It includes both intentional and unintentional components, and both intrinsic and extrinsic processes, such as emotional awareness, identification and acceptance, the generation of new emotional experiences, the reinterpretation of distressing cognitions and flexible modulation of emotional responses in order to meet situational demands [108]. Emotional regulation undergoes specific developmental age-related changes from childhood to adulthood, when strategies become more flexible, coherent and adaptive. Emotional stability seems to be particularly low in adolescence (showing the most limited repertoire of emotional regulation strategies), but it has not yet become established in emerging adulthood, either [104]. Managing emotions adaptively is central for social adjustment and individual psychological well-being, and emotional dysregulation is related to the development and maintenance of various psychopathological conditions in children, adolescents and adults [108]. Emotional regulation failures are a well-recognized hallmark of drug addiction [17], with poor regulation abilities creating a predisposition to use drugs and to eventually develop an addictive disorder. Khantzian [48] was the first to propose that individuals rely on drugs as a means to alleviate aversive emotional states and to increase positive affects. This might be particularly true in adolescence and youth, when emotional regulation abilities are still developing and, therefore, are not yet properly mastered [85, 104].

1.2. Alexithymia

Alexithymia is a multidimensional construct, made up of emotional and cognitive components: difficulties in identifying and describing feelings, differentiating body sensations and feelings, lack of fantasy and an externally oriented cognitive style [67, 66]; overall, these characteristics reflect a deficit in the cognitive processing of emotions [35, 42, 58, 69, 92]. Interestingly, a distinction can be made between primary alexithymia, considered a personality trait arising out of early or genetic vulnerability, and secondary or organic alexithymia, which is viewed as a cognitive deficit that derives from mental illness or brain injury [63, 91]. Also, drugs, through their neurotoxic effects, may cause brain alterations that, in their turn, can lead to alexithymic traits. Although it is still controversial whether, in this circumstance, alexithymia has a primary or secondary nature and its role as a risk factor is still to be determined [18, 93, 95], it is quite common in SUDs [20, 27, 38, 54, 65, 70, 87, 98]. The role of alexithymic traits as a risk factor for SUDs can be explained as a consequence of immature self-awareness, scarce cognitive regulation of one’s emotions [93], lack of cognitive representations of neurophysiological stimuli [47], and impulsivity, meaning failures in reflective and sophisticated cognitive processes of cognitive and emotional regulation, and engaging in substance use when experiencing heightened and disturbing affects [70, 84]. Difficulties in identifying and expressing emotions are also related to increased drug use in adolescents [99], while among young substance abusers, the prevalence of alexithymia is reported to range from 30 to 43.9% in individuals aged 15-24 – recorded at higher levels than in the general population [22, 29, 28, 82, 100].

1.3. Emotional intelligence

Emotional intelligence (EI) is a multifaceted construct [90]; there are several explanatory models of emotional intelligence, among which the mental ability model highlights the association between emotions and cognition, defining it as the “ability to perceive accurately, appraise, and express emotions; the ability to access and/or generate feelings when they facilitate thoughts; the ability to understand emotions and emotional knowledge; and the ability to regulate emotions to promote emotional and intellectual growth” [62, 61]. Some models include both mental abilities and traditional personality traits, such as optimism and mood [9, 37]; it can therefore be assumed that emotional intelligence overlaps with both cognitive intelligence and personality traits [19, 102]. Low levels of EI are associated with maladjustment, including deviant behaviour, drug use, and behavioural addictions [12, 33, 50, 53, 76, 77]. The relationship between low EI and addictive disorders can be attributed to the inability to comprehend and manage negative effects [48, 97] or interpersonal problems [5], resulting in difficulties in understanding emotional causes and regulating affect at intrapersonal and interpersonal levels [16, 33]. In general, on one hand, low levels of EI contribute to the onset
of drug abuse [37, 53] and are recognized as a predictive factor for alcohol and drug-related problems [78, 83]; on the other hand, high levels predict favorable treatment outcomes, at various pre- and post-treatment levels. Similar findings emerge in studies focusing on adolescence, during which the development of several emotional capacities occurs: self-awareness of inner states, communicating emotions, appropriately perceiving and responding to others’ emotions, regulating affect, adaptively coping with problems and maintaining a positive mood [10]. With young people in their teens and early twenties, lower emotional ability correlates with adolescent deviant behaviour [64] and with the use of drugs [10, 25, 49, 99], both licit, such as alcohol [99], and illicit. A review study [50] confirms this association for several types of substances and behavioural addictions; this study, in addition, pinpoints the capacities of regulating/decoding and differentiating emotions as the most prominent factors in SUDs.

1.4. Sensation Seeking

Adolescence is distinguished by reward-related behaviours, including enhanced interactions with peers and risk-taking experiences [15, 86, 88], because the brain’s socioemotional system undergoes marked developmental change. A fundamental neurodevelopmental mechanism is the increase of dopaminergic activity in the prefrontal cortex (PFC), with important implications for the reward system, whose circuits overlap with social information processing circuitry (such as social judgments) [81]. As a consequence, adolescents are highly sensitive to peers’ influence regarding risk-taking behaviours, which occur especially in the context of the peer group. Second, according to the “dual system model” [89], adolescents’ behaviour seems to be guided mainly by affective evaluations, even in taking risky decisions. That is the reason why, even though a specific behaviour may be evaluated as dangerous (as a matter of fact, adolescents are as good as adults at evaluating risks), the associated social information can promote a positive affect that makes adolescents judge it as less risky. Moreover, because of the age factor, adolescents respond differently to rewarding stimuli (such as drugs) that exert an enhanced rewarding effect [30, 89], according to a non-linear trajectory that tends to diminish towards adulthood [45]. In this sense, a teen might use drugs to achieve an internal reward, by the regulation of emotions and changing mood, and/or an external reward, such as social approval [21]. Sensation seeking is a personality trait strictly connected with the vulnerability of adolescents towards reward-related behaviour; it is centred on the seeking of varied, novel, complex and intense sensations and experiences, and the willingness to take physical, social, legal and financial risks for the sake of those kinds of experience [105]. Results show that sensation-seeking levels are not stable, and rise during adolescence [57]. Sensation seeking correlates positively with multiple problematic and high risk behaviours, ranging from deviant behaviour, shoplifting, aggression, and unprotected sex to the misuse of legal and illegal drugs, even in adolescence and youth [1, 4, 8, 39, 59, 68, 79, 106]. More specifically, sensation seeking seems to be crucial in the early phases of experimentation with legal and illegal substances, and may lead the subject to polydrug use in the constant search for new experiences; it has also been suggested that seekers of ‘highs’/strong sensations tend to prefer stimulant drugs, in order to pursue activities and stimulations and to defeat their proneness to boredom [44]. Consequently, it is not surprising that in early adolescence sensation seeking plays a predictive role not only for drug use itself [23, 75], but for later social maladjustment, too [106]. In specifically discussing teens and young people, studies reported intense sensation seeking associated with substance use and abuse.

Among college students, sensation seeking emerged as the most effective and powerful predictor of substance misuse; it has also been indicated as one of the most important motives for taking drugs [46]. According to a large-scale study on adolescents (aged 13–18), 80% presented elevated levels of sensation seeking [60]. The high frequencies reported for sensation seeking in young adulthood can be explained as being due to the adoption of a biosocial model [80]. Quite recently, in 2013, a direct association between risk taking and white matter integrity has been attested in substance-abusing youths, with frontolimbic matter integrity proving to be a strong predictor of risky behaviours [45].

The present study has the aim of evaluating the main characteristics of drug-addicted young adults’ emotional functioning and its possible dysregulation, with respect to alexithymia, sensation seeking and emotional intelligence.
2. Methods

2.1. Sample

Sixty-eight subjects, aged 18-24, were recruited in a residential Therapeutic Community for Substance Use Disorders, and in high schools and colleges in Italy. The sample comprised a clinical group (N=41) and a comparison group (N=27).

The clinical group adopted the following inclusion criteria; participants should: a) meet the DSM-IV-TR [2] criteria for Substance Use Disorder; b) be referred and admitted to the residential treatment community for less than 3 months. 54% of the sample were males and the mean age was 21 years (± 2.1). Most of the participants were unemployed. Many young inpatients (48.8 %) reported that one or both of their parents had suffered or were still suffering from a past or current Substance Use Disorder (SUD). It is worth noting that a high percentage (54%) had experienced potentially traumatic experiences in their past (such as maltreatment, sexual or physical abuse). At the start of the study, subjects in the clinical group had been abstinent from drugs for an average of 3 months.

The control group was selected by matching subjects with the normative group. OAS was not administered to subjects in the comparison group, given the fact that no caregiver figure or close adult acquaintance was included in data collection.

The Observer Alexithymia Scale (OAS; [40]). An observational measure of alexithymia is fundamental in order to overcome a limit of self-report tools for this construct, because self-report questionnaires require respondents to report on a capacity they may lack because of the low rates of self-awareness they have on this problem [52, 56, 103]. The OAS is a 33-item observational scale, to be completed by a subject’s relative or acquaintance (in the specific case of this study it was administered to individual psychotherapists). Items are rated on a 4-point scale and tap five alexithymic features: Distant (being unskilled in intrapersonal and interpersonal issues), Uninsightful, Somatizing, Humourless and Rigid. The scale revealed good psychometric characteristics [28, 40, 41, 96]. OAS was not administered to subjects in the comparison group, given the fact that no caregiver figure or close adult acquaintance was included in data collection.

Bar-on Emotional Intelligence Inventory (EQ-i; [34, 9]). EQ-i is a self-report tool designed to evaluate emotional intelligence based on Bar-On’s model [9]; the instrument was developed from a conceptualization of EI as a combination of abilities, competences and skills that include emotional awareness, impulse control, problem solving, optimism and interpersonal relationships [9]. In fact, the inventory identifies 5 major factors or scales (Intrapersonal, Interpersonal, Adaptability, Stress Management, General Mood) and 15 subscales. 133 assertions are rated on a 5-point scale from 1 (“it never or rarely applies to me”) to 5 (“it very often or always applies to me”). It gives an overall total score, referred to as Emotional Quotient, and a score for each composite scale and subscale. Interestingly, empirical evidence proved that EQ-i is a reliable measure [26], and its results can serve as a predictor of drug use [11] and an adequate measure of treatment efficacy.

Sensation Seeking Scale – form VI (SSS-VI). Since its introduction, this tool has been considered the standard measure for sensation-seeking traits. It is a self-report questionnaire comprising separate scales, with the aim of independently evaluating actual and
desired experiences for two sensation-seeking factors, namely: Thrill and Adventure experiences, and Disinhibition experiences [36, 105]. The instrument includes a first part, with 80 items describing disinhibition together with thrill and adventure experiences referred to in the respondent’s past, called Experiences of Thrill and Adventures (ETAS) and Experiences of Disinhibition (EDIS), respectively. The respondent has to indicate if he/she has actually engaged in the activity described, that is, if he/she never did it, did it once, or did it more than once. In Part II the same items are presented but now the subject has to indicate if he/she would engage in the activity in the future, reporting if it is something that he/she is not willing to do, something he/she thinks about but does not intend to do, or something he/she will do if there is an opportunity. In Part II as in Part I, items are differentiated into the disinhibition and thrill/adventure domains, namely Intentions of Thrill and Adventure (ITAS) and Intentions of Disinhibition (IDIS). The scale shows good psychometric characteristics. The comparison group only completed the first part of the questionnaire.

The collection of sociodemographic data occurred according to the standard protocol adopted by the Therapeutic Community at admission and using an ad hoc interview format. If necessary, data were integrated and/or confirmed by information reported by outpatient mental health services that referred the patient to the facility.

2.3. Data analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS) 21.0. Descriptive statistics and nonparametric tests (Pearson’s chi square test, Mann-Whitney U test, and McNemar test) were applied. As a preliminary analysis, Cronbach’s alpha coefficient was used to assess the reliability of the questionnaires (EQ-I, TAS-20, OAS, SSS-VI) (Table 1).

3. Results

The total scale of each instrument showed from good to very good reliability (.801 ≤ α ≥ .962); all the subscales included in TAS-20, OAS, EQ-i and also SSS-VI demonstrated levels ranging from acceptable
to very good (0.649 ≤ α ≥ 0.940), with only two exceptions: the Concrete Thinking scale in TAS-20 and the Humourless scale in OAS, which were excluded from further analysis.

3.1. Emotional functioning

With respect to alexithymia, using the score of 60 as cut-off for the TAS-20, a dichotomous variable was computed to indicate the presence or absence of alexithymia. As regards the clinical group, 61% (N=25) of subjects reported no alexithymic traits of clinical significance (Table 2). The observed frequencies on the TAS-20 subscales showed that 58.5% of young inpatients had scores with 1 standard deviation above the mean on the Difficulty in Identifying Emotions (F1) scale, while the other scale, Difficulty in Describing Feelings (F2), showed considerably lower percentages, with an overall value of 34.1%. As regards the OAS measure, the adoption of categorical variables made it clear that alexithymia is a distinctive trait of a high proportion of drug-addicted youth (82.9%), according to their psychotherapists. From a descriptive point of view, critical results (more than 1 standard deviation above the mean) were detected on the Distant (D) and Insightful (U) scales, with rates of 78% and 70.7%, respectively [Table 3].

In order to compare the self-report measure of alexithymia (TAS-20), which was administered to patients, with the observational assessment (OAS), which was administered to individual psychotherapists, the nonparametric McNemar’s test was used, highlighting a significant difference in paired proportions, with clinicians reporting higher percentages of alexithymic individuals [McNemar test, p=0.000].

When the presence/absence of alexithymic traits were considered dichotomously, very few young people without SUDs attributed to themselves any alexithymic traits (7.4%). The chi square test revealed a significant difference between the two groups, indicating that a higher rate of young people with SUDs showed clinically significant Difficulty in Identifying Emotions ($\chi^2 = 5.460, p = .025$) and, more in general, were categorized as alexithymic on the TAS-20 total score ($\chi^2 = 8.361, p = .005$). Similar results emerged when the Mann-Whitney U Test was applied; both concerning the ability to comprehend one’s affective states (Difficulty in Identifying Emotions scale; $z = -3.452, p = .001$) and the overall alexithymic traits (TAS-20 total scale; $z = -3.055, p = .002$) young non-addicts ascribed to themselves fewer emotional problems. In both cases, results remained significant for the Bonferroni correction ($p=.05/2=.025$).

As regards emotional intelligence, observing the frequency distribution obtained on the EQ-i, 70.8% young drug-addicts showed Stress Management competence below average, and 65.9% on the General Mood scale. It is worth noting that only a small por-

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<th>Table 2. Alexithymic traits</th>
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tion of inpatients ascribed to themselves difficulties in the interpersonal domain. Still, overall emotional intelligence turned out to be below the normative range for 61% participants of the clinical group, as illustrated in table 3. Conversely, only a small proportion of non-addicted youngsters (11.1%) reported an insufficient emotional quotient. For all the subscales, less than 30% of non-clinical subjects reached an insufficient level of emotional abilities. The rates of individuals with low emotional competences were compared in the two samples, with the Pearson’s chi square test adjusted for multiple comparisons. On two scales, Stress Management ($\chi^2 = 12.518$, $p = .001$) and General Mood ($\chi^2 = 16.418$, $p = .000$), and on the overall Emotional Quotient ($\chi^2 = 16.712$, $p = .000$) the group of drug addicts revealed higher frequencies of subjects with emotional problems. Conversely, the Mann-Whitney U Test and the Bonferroni correction ($p = .05/5 = .010$) attested lower emotional competences among inpatients on the Intrapersonal ($z = -3.144$, $p = .002$), Interpersonal ($z = -3.043$, $p = .002$), Stress Management ($z = -3.737$, $p = .000$) and General Mood ($z = -3.466$, $p = .001$) subscales, together with the total Emotional Quotient ($z = -4.541$, $p = .000$).

Results in table 3 point out that the majority of participants (87.8%) showed high levels of sensation seeking (more than 1 standard deviation above the mean), having engaged in the past in at least one type of risky behaviour, in terms of adventure (ETAS) and/or disinhibition (EDIS) experiences. In greater detail, 42.8% of participants reported a number of past experiences of thrill and adventure (ETAS), but even more subjects, as many as 82.9%, reported a high number of experiences of disinhibition (EDIS). Most of these individuals did not show any significant intention to get involved either in adventure (ITAS) or disinhibition (IDIS) experiences in the future. In the control sample, lower percentages of individuals reported past experiences of Thrill and Adventure (16.7%) and Disinhibition (29.2%). The difference in frequency distributions and scores between the two groups was confirmed both for ETAS ($\chi^2 = 6.703$, $p = .016$) ($z = -3.654$, $p = .000$) and General Mood ($\chi^2 = 12.512$, $p = .001$) subscales, together with the total Emotional Quotient ($\chi^2 = 16.712$, $p = .000$).

The general trend in emotional intelligence in the clinical group is illustrated in table 3. Conversely, only a small proportion of non-addicted youngsters (11.1%) reported an insufficient emotional quotient. For all the subscales, less than 30% of non-clinical subjects reached an insufficient level of emotional abilities. The rates of individuals with low emotional competences were compared in the two samples, with the Pearson’s chi square test adjusted for multiple comparisons. On two scales, Stress Management ($\chi^2 = 12.518$, $p = .001$) and General Mood ($\chi^2 = 16.418$, $p = .000$), and on the overall Emotional Quotient ($\chi^2 = 16.712$, $p = .000$) the group of drug addicts revealed higher frequencies of subjects with emotional problems. Conversely, the Mann-Whitney U Test and the Bonferroni correction ($p = .05/5 = .010$) attested lower emotional competences among inpatients on the Intrapersonal ($z = -3.144$, $p = .002$), Interpersonal ($z = -3.043$, $p = .002$), Stress Management ($z = -3.737$, $p = .000$) and General Mood ($z = -3.466$, $p = .001$) subscales, together with the total Emotional Quotient ($z = -4.541$, $p = .000$).

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3.654, p = .000) and EDIS (χ² = 17.786, p = .000) (z = -5.637, p = .000) factors, respectively. Results remained significant when adjusted for multiple comparisons.

4. Discussion

The present study supplies preliminary evidence that drug addiction in youths may be associated with emotional dysregulation. To our knowledge, apart from the studies by Dorard and colleagues [28, 29], this is one of the few studies on alexithymia in drug-dependent youths in which self-reports and observational measures have been compared. According to the observational assessment, a high proportion of addicted youths revealed clinical levels of alexithymia, especially in terms of poor insightfulness and distant attitudes towards feelings and relationships. A substantial proportion of alexithymic individuals was detected by previous studies on drug-abusing adolescents [28, 29]. The self-report measures of alexithymia attested, however, that only a small proportion of inpatients attributed alexithymic traits to themselves, and the comparison between self-reporting and observational results indicated that young drug-dependent inpatients were scarcely aware of their difficulties in handling inner states. The present data are in line with the lack of correspondence between OAS and TAS-20 scores that was observed in a previous study [28], so supporting the need for observational measures to overcome the limits inherent in self-reports on critical topics that respondents might underestimate [52, 56, 103]. Speaking from a clinical perspective, the important finding of a lack of self-awareness about one’s own emotional problems might be attributable to the fact that, at the time of assessment, inpatients were at the very beginning of their treatment programme, when they were still partly unaware of their condition and its potential causes.

Unfortunately, the third TAS-20 factor (Concrete Thinking) did not reach a sufficient level of reliability, in a way similar to previous studies on substance abusers [20, 96]. According to the hypothesis of La Ferlita and colleagues [51], this result may be due to the likelihood that young adults, as well as adolescents, might struggle in making a cognitive appraisal of affective stimulus.

Emotional dysregulation further implies lower levels of emotional intelligence for drug addicts than their non-addicted counterparts; the difficulties to be faced are quite pervasive and involve several factors, especially Stress Management (which refers to difficulties in managing stressful and emotionally activating situations, regulating affects and controlling impulsive behaviours) and General Mood (having to struggle to establish and maintain a positive affective state characterized by an optimistic attitude and by the capacity to feel content with oneself, others, and life in general). In addition, drug abusers showed lower Intrapersonal (concerning self-awareness and self-expression) and Interpersonal (concerning social awareness and interpersonal relationships) competence.

Thirdly, it is possible to assume that drug experimentation and abuse had first occurred in the broader context of a search for adventure and disinhibition experiences during adolescence, given the high levels of sensation seeking attested by most inpatients, compared with young people without SUDs. The lack of any intention to engage in this kind of behaviour in the future may otherwise be interpreted as an index of motivation to change (given the fact that participants are inpatients in a therapeutic community) or else, as an attitude of denial that underestimates actual intentions.

Problems with emotional functioning tend to contribute to delineating a clinical profile of remarkable severity that constitutes a potential obstacle to treatment and a possible risk factor for relapse, given the individual’s poor ability to handle emotions and exert adequate cognitive control over disinhibited behaviours, especially in stressful situations. Alexithymia, like other defective socioemotional skills [33, 43], can be considered an obstacle to substance abuse treatment efficacy, because it implies poor treatment outcomes, attendance, therapeutic alliance and a high relapsing rate, presumably because of the low interest in introspection and reflective abilities that alexithymia implies [7, 20, 55, 95].

This study has some limitations. First, the small size of the samples does not allow results to be generalized. Second, it was not possible to establish a temporal link between drug misuse and emotional dysfunction, nor can it be ruled out that drug addiction may have impaired emotional functioning in our sample.

5. Conclusions

Our results suggest that drug dependence in young adults is characterized by difficulties in emotional regulation, indicating the importance of specific and new treatment methodologies.
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Contributors
MP, AS, PC, MS, SB, AGIM, SC, CT and LC have made a substantial contribution to the conception and implementation of the work, taking part in data acquisition, analysis and discussion, drafting and revising the manuscript. All the authors revised and reached an agreement on the final version of the work.

Conflict of interest
Authors state no conflict of interest.

Ethics
Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. All patients gave their informed consent to the anonymous use of their clinical data for independent studies.

Note
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Neuropsychological deficits in young drug addicts

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Summary

Background: Adolescence is a highly vulnerable age for experimenting with drugs; increasing evidence attests that several substances might have detrimental effects on cognitive functioning in this developmental phase, when prefrontal brain areas are still immature and may actually be the main target of the neurotoxic effects of drugs. There are still, in any case, too few studies that specifically address early adulthood.

Aim: The present study aims to investigate neuropsychological performance in young drug addicts in residential treatment (aged 18-24).

Methods: 41 young drug addicts, after admission to residential treatment, were compared with 27 subjects in the control group. A battery of neuropsychological tests (Brief Neuropsychological Exam-2) was administered to detect possible cognitive impairments. Descriptive and non-parametric statistics (Pearson’s chi square test) were performed.

Results and conclusions: Findings suggest that drug dependence in youth is distinguished by neuropsychological deficits, in particular, attention and executive function impairments – issues that now call for tailored and innovative treatment approaches.

Key Words: Emerging adulthood; drug addiction; neuropsychological functioning

1. Introduction

It is widely acknowledged that drug abuse has a neurotoxic effect on several brain circuitries that leads to structural and functional changes, mainly in the dopaminergic mesolimbic system of reward, but that also causes a cascade of neuroadaptations [52]. Consistent empirical evidence establishes that the structural and functional changes consequent on prolonged substance abuse mediate severe neuropsychological deficits; this has been attested even in adolescence and youth [11, 31], since important neurodevelopmental processes take place during the developmental period and continue until emerging adulthood [13, 23, 24], making the adolescent brain particularly vulnerable to disruptive factors.

The exposure to neurotoxins that is introduced through the use of alcohol and drugs exerts an adverse influence on the structural and functional development of the brain, especially at the expense of the corpus callosum, hippocampal and prefrontal cortex regions [62], so leading to neuropsychological impairments that primarily affect memory, attention and executive functions, often exerting a long-term influence [58]. It is, in any case, important to mention the need for caution in interpreting these results: the causal and temporal relationships between prior risk factors, substance abuse, and cognitive deficits still have to be determined, whereas it can be assumed that neuropsychological impairments pre-exist, exacerbate, and/or follow substance use [62].

Alcohol Use Disorders (AUDs) in adolescence and emerging adulthood are associated with deficits in several cognitive domains, and predict an increase in impulsive behaviour [35]. Impairments have been demonstrated for verbal and non-verbal memory [9].
attention [57], processing speed [38], visuospatial abilities [27], executive functions [22], and language skills [45].

With regards to the neuropsychological consequences of cannabis use, it has been posited that the domains of psychomotor speed, attention [34, 59], memory [5, 59], cognitive inhibition [34], verbal learning, spatial working memory [28], and executive functions [25, 51, 54] are all affected.

Cocaine-abusing adolescents have shown impairments in executive control, attention, cognitive abstraction processes, visuospatial skills, psychomotor speed, and short-term memory [4, 10, 30, 55, 63].

Apart from the above substances, nowadays, ketamine (N-methyl-D-aspartic acid; NMDA), one of the most common NMDA receptor antagonists, is a mainstream club drug. Both a large-scale study [43] and longitudinal research [44] conducted on young adults have demonstrated cognitive impairments in high-frequency users, at the expense of memory and planning functions, and they have also detected an association between the trend of ketamine use over time and a worsening of neuropsychological performance. Moreover, the use of MDMA during the teens and young adulthood leads to diminished performance over time in coping with complex, divided, and selected attention and memory tasks, so causing significantly prolonged reaction times [29]. In responding to a battery of neuropsychological tests, young users of MDMA and cannabis display cognitive impairments in performing a number of cognitive tasks (memory, learning, speed of processing) [14].

Several studies have focused on opioids and heroin. According to Davis et al. [15], 60% of opiate users show neuropsychological impairments, even though it is not clear if the deficits found are focal or diffused. It is primarily memory and the spectrum of executive functions that appear to be impaired [61, 60], involving deficits in impulse control, planning, problem solving, and implying a characteristic perseverative behaviour pattern [17, 18, 36, 46, 49]. Prefrontal cortex and limbic abnormalities have been detected in this population [17, 33, 50]. Many studies on opioid dependence have also investigated deficits in decision-making abilities, a cognitive domain that combines executive and emotional components, indicating an impaired performance in opioid users, in terms of risky decisions that have negative long-term consequences [7, 17, 20, 61]. As it is, the studies available so far have almost exclusively addressed the performance of adults, so that further evidence specifically addressed to adolescent and emerging adulthood is needed.

Other studies have addressed polydrug use. Adolescents who abuse multiple drugs show impairments in executive control, attention, abstract reasoning, visuospatial capabilities, psychomotor speed, and short-term memory performance [58]. Adolescent polyusers of alcohol and marijuana performed significantly worse than controls on cognitive tests regarding intellectual capacity, perceptual speed, language and attention [57].

The existing literature mainly focuses on adolescence or full adulthood, while it is limited on emerging adulthood. Moreover, there are still too few studies on groups of individuals whose SUD rises to a level of severity that requires inpatient treatment, and this is particularly true of the Italian context. The purpose of the present preliminary study was to investigate the neuropsychological profile of young, drug-dependent inpatients who started abusing drugs in adolescence, in order to determine if they might be suffering from cognitive impairments.

2. Methods

2.2. Sample

The present research initially involved 68 people emerging into adulthood, aged 18-24, divided into a clinical group and a comparison group. The collection of clinical data occurred as part of a broader research project (Psychological Assessment & Treatment With Addicted Youth [P.A.T.W.A.Y.]).

The clinical group was recruited in the years 2013-2015 in a residential Therapeutic Community for Substance Use Disorders named “Villa Renata, Comunità di Venezia,” located in Venice, Italy. The following inclusion criteria were adopted: a) meeting DSM-IV-TR [1] criteria for Substance Use Disorder; b) being referred to, and then admitted to the residential treatment community for less than 3 months; c) age ranging from 18 to 24 years. The administration of the assessment tools occurred approximately 2 months after their admission (M=1.4 months). 41 young inpatients took part in the study. As regards participants’ past history of drug use, as a general rule they first experimented with drugs (often, but not exclusively, with alcohol and marijuana) in early adolescence (on average at 14 years), while the onset of cocaine and heroin use occurred on average at 16 years (± 1.9). Most of them were polydrug users (80.5%), using various synthetic drugs (78%), but they indicated heroin as their primary substance.
of abuse in 75.6% of cases. In addition, the use of non-prescribed drugs is quite common, with 51.2% of these subjects having used methadone procured illegally. At the time of recruitment, participants had been abstinent from drugs for 3 months on average, as verified by urine tests. 46.6% overdosed from one to three times in the past and 24.4% had been diagnosed with hepatitis C. None of them presented other relevant medical conditions, or any other full-blown psychiatric disorders apart from SUD. In relation to treatment, the participants’ first contact with outpatient services for SUDs occurred on average at 18 years (± 2.3), that is, about two years after initiating the use of hard drugs such as heroin and cocaine. 41.5% of them had previously attended an inpatient treatment but had not concluded it. Pharmacotherapy (mainly benzodiazepines, SSRI, neuroleptics) was prescribed for most of them (84.2%).

The comparison group included 27 young people, who had been contacted as students of evening or day high schools. The main selection criteria used in the collection of these data were a) the absence of SUDs diagnosis and current drug use; b) age in the 18-24 range; c) low educational level; d) gender, in order to collect a comparison group as closely comparable as possible with the clinical one. These criteria were established primarily according to indications provided for the assessment of neuropsychological functioning, whose normative range depends on age and years of education.

2.3. Instruments

The collection of sociodemographic and drug history data was performed by applying an ad hoc interview format that conforms to the standard protocol adopted by the Therapeutic Community for all patients at admission. When necessary, data were integrated and/or confirmed by information reported in records provided by the outpatient mental health services that referred the patient to the facility.

A neuropsychological assessment protocol was administered individually to each participant; it usually took about an hour and a half.

Esame Neuropsicologico Breve-2 [Literal translation: Brief Neuropsychological Examination-2] (ENB-2; [41]), which is a comprehensive neuropsychological battery standardized for the Italian population. It includes 16 subtests (Digit span, Immediate and delayed recall prose memory, Interference memory at 10 and 30 seconds, Trial Making Test part A and B, Token test, Word phonemic fluency, Abstract reasoning, Cognitive estimation, Overlapping figure, Spontaneous drawing, Copy drawing, Clock drawing and Ideative/ideomotor praxis tests). The ENB-2 allows us to investigate several cognitive abilities: attention (TmtA, TmtB), memory (digit span, logic story-immediate recall, logic story-delayed recall, interference memory at 10- and 30-second tests), executive functioning (TmtB, cognitive estimation, abstract reasoning, phonemic fluency, clock drawing, overlapping figures), perception (spontaneous drawing, copy drawing), praxis abilities (ideative and ideomotor praxis test) and comprehension (token test). The battery provides a score for each cognitive test and a total score too, called the Global Cognitive Index. Age (15–20, 21–30 years) and education (lasting less than 9 years and at least 9 years) are the two criteria used to identify subgroups of individuals and their respective normative scores. The 5th percentile was used to determine cut-off scores for each subgroup; according to the cut-off score, performance is classified as belonging to one of the three categories: below average, borderline and above average. The battery shows good psychometric characteristics, revealing good differential validity in discriminating normative and clinical groups and sufficient test-retest reliability [42].

2.5. Data analysis

Data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) 21.0. Qualitative analysis was carried out using descriptive statistics, while for the quantitative analysis, due to the small number of subjects, non-parametric tests were applied (Pearson’s chi square test).

3. Results

Inpatients were 53.7% males (N=22) and 46.3% (N=19) females; the mean age was 20.9 years (± 2.2). 10 years (± 1.8) was the average duration of school attendance in this group; moreover, 80.5% had repeated at least one grade at school and, more interestingly, 73.2% had dropped out of school before concluding compulsory education. A majority of participants were unemployed (63.4%) and were relying on illegal activities to provide their main economic support, often incurring legal injunctions. One or both parents of many young inpatients (48.8 %) had themselves been affected by a past or current Substance Use Disorder, besides which 38.5% had been exposed to alcohol or drugs when still in the womb. In addition, as re-
gards the childrearing environment in which they had grown up, a high percentage (53.7%) had experienced maltreatment, including sexual or physical abuse during childhood and/or adolescence.

The group of young non-addicts included 37% males (N=10) and 63% females (N=17), whose mean age was 19.44 (±1.9). As regards education, the mean duration of school attendance was 10.44 years (±1.2) at the time of assessment, with 66.7% of individuals who had not yet completed compulsory education, reporting middle school as their final educational level.

The neuropsychological performance of participants on the ENB-2 battery was codified into 3 categories (below average, borderline and average); in addition, a fourth, ‘altered’ category was computed, to include subjects whose performance was at the limit or definitely impaired.

As reported in Table 1, results showed that 56% of drug-dependent patients had an impaired global cognitive profile at ENB-2, considering both those whose Global Cognitive Index reached the limits of expected levels and those who had fully impaired neuropsychological functioning. Observing the performance on the single tasks included in the battery, a high percentage of young inpatients showed an impaired performance in carrying out the following tasks: Tmt-B (56%), memory task Logical Story – Immediate Recall (46.3%), Cognitive Estimation Test (41.5%) and, even if to a lesser extent, the task called Clock Drawing (36.6%), Interference memory at 10 seconds (34.1%) and Logical Story – Delayed Recall (31.7%).

From a qualitative perspective, the neuropsychological performance of the majority of individuals in the comparison group (81.5%) fell into the normative range for age and education. Nevertheless, some cognitive tasks showed quite high rates of individuals who gave an altered performance, namely in carrying out the Cognitive Estimation (48.1%), Phonemic Fluency and Interference Memory tests in 10 seconds.
4. Discussion and conclusions

This preliminary study has been designed as a contribution to the knowledge of drug addiction in young adulthood, in particular, to a better understanding of neuropsychological functioning in inpatients aged 18-24.

Our examination of participants’ neuropsychological functioning highlighted the fact that a high proportion of young drug-dependent individuals, who were mainly heroin-addicted, showed a impaired cognitive profile, to a greater extent than their peers in the comparison group. From a focal perspective, neuropsychological impairments occurred mainly at the expense of attention and executive functions assessed with Tmt-A and Tmt-B. The latter is widely used as a measure of cognitive flexibility; it provides information about the speed of processing and executive functioning, as well as complex, divided and selected attention [3]. Results are in line with the empirical evidence presented above, which recognizes an association between cognitive deficits and the misuse of several different drugs [e.g. 14, 18, 44, 54, 63], even if empirical evidence on young opioid users is very limited, particularly in the Italian context.

Given the absence of a perspective design, no assumptions should be made about the origins of these deficits, which may either be subsequent to substance abuse or pre-existing it, or be related to other previous clinical/risk conditions, such as Attention Deficit Hyperactivity Disorder (ADHD) and intrauterine drug exposure, [21, 32, 40, 53]. It is noteworthy that a considerable number of young people in the comparison sample showed an altered level of performance in a few tasks, namely the Cognitive Estimation test (designed to assess the capacity to answer a question for which relevant knowledge, but not the specific answer, is available) and Phonemic Fluency (a task involving vocabulary size, lexical access speed, updating, and inhibition ability) as regards executive function, and Immediate Recall and Interference memory at 10 seconds as regards memory abilities. These data could be explained by considering in greater depth other variables, such as socioeconomic status, rearing environment and traumatic experiences, which are capable of compromising optimal cognitive functioning, [6, 16, 19, 26, 39, 47], besides individual and sociorelational adjustment [13, 23, 12, 56]. Moreover, other methods of drug testing would provide more reliable information about drug use than self-reported answers [37].

Intact cognitive abilities, in particular executive functions, are crucial for a goal-directed and controlled behaviour that underpins individual adjustment. In the case of drug addiction, growing evidence indicates that cognitive impairments may negatively affect treatment [48], and may be long-lasting. Even after long-term recovery, the cessation of drug use is unable to fully restore cognitive functioning [54, 27; 58], and impairments are detected even after years of abstinence from opioids [7, 18]. Thus, restoring and potentiating these abilities in drug addicts, especially if they are young, emerges as a priority. In fact, developmental neuroscience reports that the brain developmental changes are not fully completed until reaching the age of approximately 25 years, in particular in the prefrontal cortex areas, so offering a window of intervention opportunity [62, 2]. Thus, neuropsychological rehabilitation may be considered as an additional treatment to traditional protocols (based on educational and psychotherapeutic interventions) provided to young drug addicts, who would then be placed in the position to fully benefit from standard programmes. This might help in counteracting the present worrying levels of treatment dropout and poor outcome [8]. Unfortunately, despite the recognition of their importance, cognitive abilities play a peripheral role in clinical practice and, to date, only a few studies have been made available on the idea- and implementation of treatment programmes that address the issue of cognitive impairments in the population of drug addicts, which now call for further research [18].

The preliminary nature of the research and the small size of its samples are the main limitations of the study, imposing caution in drawing conclusions. The high degree of specificity of the clinical sample – made up of young adults whose SUDs was severe enough to require inpatient treatment – can be considered both as a source of strength and as a limita-
tion of the study. Moreover, as mentioned earlier, the study does not allow any speculation about temporal sequencing and causality between drug misuse and neuropsychological phenomena.

References


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Authors state no conflict of interest.

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Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study does not require ethics committee approval because it was carried out according to a non-interventional protocol. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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The influence of Comorbid Personality Disorder on patients in Heroin-Assisted Treatment: Pilot data on clinical outcome

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Summary

Background: The diagnosis of a comorbid personality disorder (PD) is very common in patients with drug dependence. However, it is unclear whether differences between opioid-dependent patients with and without co-occurring PD influence diamorphine-assisted substance abuse treatments. Methods: Twenty-six patients with a diagnosis of opioid dependence (according to DSM-IV) in a stable heroin-assisted treatment (HAT) were included in this pilot study. The SCID II was used to assess the personality disorder diagnosis. At baseline, history of substance abuse (ASI), depressive symptoms (BDI) and childhood trauma (CTQ) were measured. At a 12-month follow-up, the clinical course was assessed with the Opiate Treatment Index (OTI), and substance abuse as well as depressive symptoms were newly assessed. Results: Fifty percent (n = 13) of the patients were diagnosed with at least one personality disorder. Patients with co-occurring PD experienced more depressive symptoms at baseline (p <0.05), were more traumatized (p <0.01) but had a shorter treatment history of heroin-assisted treatment (p <0.05) and less cannabis abuse (p<0.05) than those without a PD. At the 12-month follow-up, patients with comorbid PD showed worse overall psychological adjustment (p <0.01). Conclusion: Patients with co-occurring PD had more severe psychopathological symptoms. These findings indicate that even within a heroin-assisted treatment group, patients with opioid dependence suffering from an additional PD may represent a sicker clinical subgroup, which could benefit from disorder-specific treatment.

Key Words: Addiction; opioid dependence; personality disorder; Antisocial Personality Disorder; heroin-assisted treatment; diamorphine; Substance Use Disorder; comorbidity.

1. Introduction

It is well known that psychosocial and physical impairments are common among patients with substance abuse. In recent years, several studies have focused on the relationship between drug addiction and other mental disorders. A high prevalence of comorbid psychiatric symptoms in patients with substance use disorders (SUDs) has been a consistent finding [26, 28, 34]. In opioid dependence, a chronic relapsing disorder that is characterized by a compulsion to seek and use opioids [30], affective disorders and personality disorders (PD) are the most widespread comorbid types of mental disorder [7, 18, 48].

Several authors have suggested that affective instability and impulsivity underlie the development of both conditions — PD and SUD — and thus explain much of their comorbidity [6, 45]. Furthermore, both PD and SUD are often associated with early adverse life experiences (e.g., childhood physical/sexual abuse and a dysfunctional family), which may also contribute to the development of psychopathology [8].

Comorbid PDs occur in about 60% of individuals with substance abuse [25, 37, 44]. PDs of Cluster B (Borderline PD, Antisocial PD, Histrionic PD,
Narcissistic PD) are those most frequently diagnosed [25, 35, 44]. The relevance of antisocial PD (ASPD) in SUD has already been shown: antisocial behaviour is a predictor of developing opiate dependence, and ASPD is related to multiple substance use [23]. To date, however, other than ASPD, the association between SUD and PD has been little investigated prospectively, so prospective outcome evaluations are important. In addition to the findings on ASPD, recent work has demonstrated the important role of borderline PD (BPD) and schizotypal PD in the course of co-occurring SUD [21, 53]. Moreover, even patients with remitted BPD were shown to have a high vulnerability to substance relapse [53].

Although a lifetime diagnosis of a comorbid mental disorder does not seem to affect the long-term course of opioid dependence linearly [50], personality pathology is a serious problem in opioid-dependent patients. Personality disorders have a major negative impact on patients’ subjective quality of life, including their physical, mental and social functioning [14, 24, 41]. Moreover, comorbid PD in patients with SUD was found to be associated with a greater involvement in the following factors: illegal drug use, psychopathology, impulsivity, aggressive behaviour, isolation and depressiveness [37], as well as in greater global impairment [44]. Those with opiate addiction often manifest antisocial temperament configuration (a high level of novelty seeking, difficulties in reward dependence). Patients with opioid dependence and with PD differ significantly in their interpersonal style [11] and their personality profile [14] from those without PD, as was to be expected.

In summary, the research literature provides evidence that comorbid PD, especially BPD and ASPD, renders the psychopathology and clinical outcomes of SUD more serious [27, 31, 32, 36, 54, 56]. Addiction severity and psychiatric comorbidity explain the greatest amount of Quality of Life variance in a clinical sample of patients with alcohol, drug and dual dependence [10]. Other studies do not support the notion that individuals with BPD and SUD display more severe BPD features than individuals with BPD alone [29]. Overall, a certain paucity of evidence remains about whether comorbid PD exacerbates SUD features and generates greater psychopathology.

Thus, the aim of the current study has been to compare opioid-dependent patients receiving heroin-assisted treatment, with and without a comorbid personality disorder, in terms of psychopathological symptoms at baseline and clinical course of illness at a 12-month follow-up.

We tested the following specific hypothesis: that despite a stable heroin-assisted treatment with closely comparable setting variables, patients with opioid dependence and with PD would score higher than those without PD in depression symptoms and lower in psychological adjustment.

2. Methods

2.1. Study sample

Twenty-six patients (17 male, 9 female) were included from among patients of the University of Basel Psychiatric Hospital’s Division of Substance Use Disorders (heroin-assisted treatment, HAT). They were aged 23-58 years (mean age = 41.0, SD = 6.8), met the DSM-IV diagnostic criteria for opioid dependence, and had been in HAT for a mean period of 6.9 years (SD = 4.5). All patients got regular supportive meetings (during the 12-month follow-up period too) with mental health workers, but no specialized or manual treatment for PD.

The sample was part of an experimental study design with n=28 heroin-dependent patients. N=2 were missing according to the SCID II testing; for details, see [52]. Exclusion criteria included a positive breath-alcohol test and a history of major mental disorders (other than SUD and PD) (e.g., schizophrenia). All patients received written information on the examination protocol and gave their written consent. The study was approved by the local ethics committee (EKBB).

2.2. Procedure

At baseline, the personality disorder diagnosis was assessed by applying the German version of the Structured Clinical Interview for DSM-IV, Axis II (PD); SCID-II [15, 17, 55]. Interviewers were first trained to improve their reliability. Prior to this study, personality disorder diagnosis had not been evaluated with a standardized instrument, although patients had been in the treatment for many years. When heroin-maintained patients fulfilled the inclusion criteria, their history of heroin and other illicit substance use was assessed by applying the semi-structured interview according to ICD-10 research criteria.

At a 12-month follow-up, the Opiate Treatment Index (OTI) [12] was used to assess the course of patients’ substance use and related problems. To evaluate changes, the Addiction Severity Index (ASI) [43] as well as the Beck Depression Inventory (BDI) [2]
were used once again.

2.3. Clinical measurements

The SCID-II is a two-stage instrument for assessing PDs. It consists of a screening questionnaire and a structured interview. Its excellent inter-rater reliability varies between 0.77 and 0.94 (the mean kappa value for all PD = 0.84), indicating that the SCID II provides a reliable and valid tool for diagnostic purposes in clinical practice as well as in research [33].

The Opiate Treatment Index (OTI) is a multidimensional instrument for evaluating the effects of opiate treatment. It includes six scales, which assess the following independent outcome domains: drug use, HIV risk-taking behaviour, social functioning, criminality, health and psychological adjustment. For each of the scales, an alpha coefficient of \( \alpha = 0.38 \) – 0.83 was calculated. Correlations with the Addiction Severity Index (ASI) [43] provided a validity of 0.42-0.70. As the OTI has excellent psychometric properties, it can be used as a reliable and valid instrument for both clinical and research goals [12].

Depressive symptoms were measured by applying the Beck Depression Inventory (BDI) [2, 22]. The Childhood Trauma Questionnaire (CTQ) [1, 3] was helpful in assessing the number and severity of patients’ trauma experiences. Both instruments are well-established tools for determining clinical symptomatology.

2.5. Statistical analyses

For comparison of means, the Student t-test and, where appropriate, a non-parametric test (Wilcoxon signed-rank test) for independent samples were used. Frequencies were analysed by means of the Chi-square test (Fisher’s exact test). All analyses were computed by utilizing the statistical programme SPSS 19.0. Graphs were created with SigmaPlot 11.0. The two-tailed significance level was set to \( p<0.05 \). Power analysis indicated that the number of patients was sufficient for detecting probabilities of 80% (for \( R= 0.7 \)) or 95% (for \( R = 0.8 \)).

3. Results

3.1. Sociodemographic and clinical variables at baseline

Half of the patients (n=13) were diagnosed with an additional PD; the majority revealed an antisocial PD (see Table 1). No significant differences were observed in sociodemographic variables, but patients

<table>
<thead>
<tr>
<th>Table 1: Socio-demographic and clinical characteristics of the study sample (n=26) and subdivided for patients with and without a co-occurring personality disorder (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n=26)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Relationship, n (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Education in years, mean (SD)</td>
</tr>
<tr>
<td>Currently Employed, n (%)</td>
</tr>
<tr>
<td>Disability pension, n (%)</td>
</tr>
<tr>
<td>Age at first-time heroin use, mean (SD)</td>
</tr>
<tr>
<td>Duration of heroin use, mean (SD)</td>
</tr>
<tr>
<td>Duration of HAT in years, mean (SD)</td>
</tr>
<tr>
<td>Doses of DAM (mg/day), mean (SD)</td>
</tr>
<tr>
<td>Current substance abuse</td>
</tr>
<tr>
<td>Cocaine, n (%)</td>
</tr>
<tr>
<td>Cannabis, n (%)</td>
</tr>
<tr>
<td>Tobacco, n (%)</td>
</tr>
<tr>
<td>Numbers of cigarettes/day, mean (SD)</td>
</tr>
<tr>
<td>BDI Sum at baseline, mean (SD)</td>
</tr>
<tr>
<td>Personality Disorders, n (%)</td>
</tr>
<tr>
<td>Paranoid PD</td>
</tr>
<tr>
<td>Schizoid PD</td>
</tr>
<tr>
<td>Antisocial PD</td>
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<tr>
<td>Borderline PD</td>
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<tr>
<td>Avoidant PD</td>
</tr>
<tr>
<td>Obsessive-Compulsive PD</td>
</tr>
</tbody>
</table>

Note. SD= Standard Deviation  HAT = Heroin-assisted treatment; DAM = Diacetylmorphine (heroin); *p<0.05, **p<0.01
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with comorbid PD scored significantly higher on the BDI depression index (p<0.05).

Looking now at various forms of substance abuse, patients with PD had a significantly shorter duration of heroin-assisted treatment (HAT) (p<0.05) and less cannabis abuse (p<0.05).

Figure 1 shows the scores for both groups on the CTQ. Patients with comorbid PD reported more emotional (p=0.049) as well as physical abuse (p=0.032), and scored higher on the total index (p=0.009). Effect sizes were large.

3.2. Follow-up after 12 months

At the 12-month follow-up, there were no significant differences in additional drug use between opioid-dependent patients with PD and those without PD (see Table 2). Patients with comorbid PD still had higher scores on the BDI, but the difference was no longer significant. However, on the OTI these patients scored significantly worse on psychological adjustment (p<0.01) and showed a slight but not significant trend towards worse social functioning (p=0.052), but with less HIV risk-taking behaviour (p= 0.057). Effect sizes were large in this case too.

4. Discussion

The present pilot study examined whether opioid-dependent patients with a co-occurring PD differ from those without a co-occurring PD in psychological characteristics, and whether they might thus constitute a specific subgroup in opioid dependence, so making possible the prediction of a clinical course.

Table 2: Clinical characteristics of the patients at 12-month follow-up

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Without PD (n=13)</th>
<th>With PD (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance abuse at 12 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis, n (%)</td>
<td>4 (30.8)</td>
<td>4 (30.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cocaine, n (%)</td>
<td>3 (23.1)</td>
<td>6 (46.2)</td>
<td>0.400</td>
</tr>
<tr>
<td>BDI Sum at 12 month, mean (SD)</td>
<td>10.2 (7.0)</td>
<td>15.7 (9.0)</td>
<td>0.097</td>
</tr>
<tr>
<td>Opiate Treatment Index (OTI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug use, mean (SD)</td>
<td>23.4 (6.1)</td>
<td>21.5 (10.2)</td>
<td>0.545</td>
</tr>
<tr>
<td>HIV risk-taking behavior mean (SD)</td>
<td>6.8 (2.6)</td>
<td>4.9 (2.0)</td>
<td>0.057</td>
</tr>
<tr>
<td>Social functioning, mean (SD)</td>
<td>12.8 (7.7)</td>
<td>18.4 (6.2)</td>
<td>0.052</td>
</tr>
<tr>
<td>Criminality, mean (SD)</td>
<td>0.2 (0.6)</td>
<td>0.6 (1.0)</td>
<td>0.204</td>
</tr>
<tr>
<td>Health, mean (SD)</td>
<td>6.9 (4.4)</td>
<td>8.2 (4.9)</td>
<td>0.481</td>
</tr>
<tr>
<td>Psychological adjustment, mean (SD)</td>
<td>16.5 (8.8)</td>
<td>28.5 (12.1)</td>
<td>0.003**</td>
</tr>
</tbody>
</table>

Note. SD= Standard Deviation ; HAT = Heroin-assisted treatment; *p<0.05, **p<0.01
In a 12-month follow-up exploration, we found significant differences between patients with and those without co-occurring PD in their psychopathological symptom burden. This was the main result of our pilot study.

In agreement with previous research [12], we found no significant differences between the sociodemographic data pertaining to patients with, and those without co-occurring PD, so suggesting that these variables were not, or at best, were less decisive, predictors of clinical severity. It is, however, true that Kokkevi and colleagues [25] found that patients with substance dependence and with a comorbid antisocial PD were significantly younger than those without a comorbid antisocial PD when they began to use illicit drugs.

Psychological status was worse in the group of patients who had opioid dependence and also had a comorbid PD. The most common PDs were Antisocial PD (26.9%), Anxious (avoidant) PD (19.2%), Borderline PD (11.5%) and Obsessive-Compulsive PD (11.5%). In this group, in accordance with our hypothesis, depressive symptoms, as well as general psychological maladjustment, were significantly more manifest than in those without any co-occurring PD. This difference turned out to be clinically relevant. Moreover, these patients showed considerably more trauma experiences. This suggests that emotional and physical abuse are especially relevant factors, not just in the etiology of SUD, but most notably in the development and maintenance of severe PD and other mental symptoms [13].

In previous research, HAT was consistently found to be an effective treatment for severe opioid dependence in a variety of countries [5, 19, 20, 38, 40, 46, 47, 49].

Interestingly, patients with opioid dependence but without co-occurring PD and showing a better overall psychological state had a significantly longer treatment history of heroin-assisted treatment (HAT). This confirms previous research findings that opioid-dependent, non-comorbid patients show higher response rates for HAT, compared with patients who have a psychiatric comorbidity [42]. Patients with personality disorders frequently drop out of therapies prematurely.

Axis II comorbidity seems to be more deleterious than Axis I comorbidity, in terms of the clinical course of opioid dependence. It is possible that a longer treatment history of heroin-assisted treatment (HAT) in patients without co-occurring PD is an indicator of higher stability and not of higher morbidity. Another explanation could be that the emotional instability that underlines the proneness to an addictive disorder belongs more to Axis-II premorbid conditions than to Axis-I full-blown pathology comorbidity.

Our pilot findings (mean duration of controlled agonist opioid treatment) indicate that HAT, with its psychosocial treatment elements and risks, may contribute to a globally successful therapy outcome even for patients with chronic opioid-dependence and with serious additional psychological problems. In addition to the reduction of substance use problems, patients’ mental state (possibly including severe psychiatric disorders like PD) seems to improve over time as well. It is unclear whether the phasic opioid stimulation provided by heroin-assisted treatment, while able to reverse withdrawal and drug-seeking behaviours, may not be able to treat important aspects of addiction psychopathology, as it is just a similar phasic opioid stimulation of street opiate use.

The following limitations in the present study must be considered: First, it could be that neither patient group was large enough to allow possible group differences to be discovered. Therefore, the small sample size in our study (N = 13 for each group) could be an explanation for the statistically less than significant results recorded for the clinical outcome variables. Furthermore, we did not discriminate between patients with different comorbid (specific PDs e.g., ASPD alone and ASPD with comorbid BPD) and important exclusion criteria (major mental disorders other than SUD and PD). Various different PDs may be accompanied by different neurobiological correlates and other disorder-specific factors [4, 39], and this could have produced a bias affecting the findings of our study. In an earlier study by our group, we found normally modulated affective reactivity (startled responses) in patients with heroin-dependence and with ASPD [51]. It could be that heroin-assisted treatment itself has an impact on the psychopathology of opioid addicts.

Lastly, the main result of our study – the differences found in 12-month outcomes – was based on only one instrument (OTI) not performed at baseline. It might therefore be true that differences in the OTI domains could have been there at baseline, before baseline, during the 12 month interval, and at 12 months (or any combination of these).

Despite these limitations, our pilot study provides initial evidence of some specific characteristics in patients with opioid-dependence and with an additional PD (especially ASPD (53.8%) in the PD
group, together with higher criminality rates), which suggests there may be clinical possibilities for the treatment of SUD. Low anxiety sensitivity could indirectly mediate the relationship between ASPD and opioid dependence.

The present investigation is a pilot study of psychological differences between patients with opioid dependence and with PD (especially ASPD) and those without co-occurring PD that are in a stable substitution treatment (HAT). In addition to the opioid substitution itself, patients with opioid dependence and with comorbid PD may draw benefits especially from broad treatment interventions, including more PD-specific psychotherapy (e.g., dialectical behaviour therapy, mentalization-based treatment, transference-focused psychotherapy, schema therapy). Moreover, treatment of comorbid PD could be an additional therapy goal in patients with SUD in the future. It was shown that BPD constitutes a high vulnerability factor for SUD relapse [53], and that it has a negative impact on the course of affective and anxiety disorders as well. The social and psychological consequences are significant, too. Patients with ASPD in methadone maintenance were over five times more likely to receive physical disability benefits than patients in methadone maintenance without ASPD [9]. ASPD is also a predictor of criminal behaviour in patients with drug abuse [16]. But the heterogeneity of the PD population is difficult to interpret meaningfully, as that population comprises quite a range of different disorders.

In order to prevent relapse in drug use, it may therefore be clinically crucial to treat the co-occurring PD in patients with SUD.

5. Conclusions

The current study suggests that, even in a heroin-assisted treatment setting, there is a specific, clinically worse subgroup of opioid-dependent patients mainly characterized by psychiatric comorbidity with PD. This confirms previous research findings and could have a relevant clinical implication, as this comorbidity should be considered in therapy [42]. However, more research should be carried out; in particular, what seems to be most needed is a fully prospective outcome evaluation that differentiates between individual personality disorders and co-occurring substance use (e.g. cocaine, marijuana) that proved to be frequent in our pilot patients even in a stable HAT, while making use of a greater number of instruments.

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Contributors

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Conflict of interest

All authors declare no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. All patients gave their informed consent to the anonymous use of their clinical data for this study.

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Incidence of cancer and cancer related mortality in opiate dependent patients treated with methadone, buprenorphine or implant naltrexone as compared with non-opiate using controls

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2. The School of Public Health, University of Sydney, Australia
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Summary

Background: Cancer has been identified as a common cause of mortality in opiate dependent patients. Aim: To examine and compare the incidence of cancer and cancer mortality in opiate dependent patients treated with methadone, buprenorphine or implant naltrexone to a cohort of controls taken from the general population. Methods: The study was a retrospective longitudinal follow up using routinely collected cancer and mortality data. Participants included opiate dependent patients treated for the first time with methadone (n=2,227), buprenorphine (n=1,954) or implant naltrexone (n=958) between 2001 and 2010 in Western Australia (WA) and a sex and age matched cohort of controls selected from the WA electoral roll. Incidence of cancer and cancer related mortality in the four groups were analyzed using Cox proportional hazard regression. Results: Rates of cancer in opiate patients treated with methadone (HR:0.81, CI:0.49-1.34), buprenorphine (HR:0.74, CI:0.41-1.33) and naltrexone (HR:0.65, CI:0.28–1.50) participants were not significantly different to the control cohort. Rates of respiratory cancer were elevated in patients initially treated with methadone (HR:7.53, CI:1.46–38.93) and naltrexone (HR:7.65, CI:1.07–54.48). Mortality rates in patients diagnosed with cancer were significantly elevated in patients treated in methadone (HR:3.19, CI:1.07–9.53), while both buprenorphine (HR:3.07, CI:0.78–12.15) and naltrexone (HR:3.73, CI:0.77–18.02) were not dissimilar to the controls. Conclusions: While rates of cancer were not significantly different to the control, poor survival may attribute to high rates of cancer related mortality.

Key Words: Buprenorphine; cancer; methadone; mortality; naltrexone; opiate dependence

1. Introduction

The use of illicit opioids has been linked with high rates of morbidity and mortality, generally associated with the direct effect of the drug or as a result of the associated lifestyle [2]. Morbidity and mortality as a result of cancer is often overlooked in opiate using populations, however cancer is a leading cause death in such patients often over taking more commonly recognized causes of death associated with the use of illicit opioids such as suicide, infectious diseases including AIDS, poisoning and injury [5, 8, 16, 17].

The increased risk of cancer has been traditionally attributed not to the opioids themselves (as demonstrated by a lack of carcinogenic effect in animal models), but to the high rates of exposures to other cancer risk factors such as increased consumption of tobacco and alcohol, high rates of infection of blood borne viruses such as HIV, hepatitis B and C, and low socioeconomic status [14]. However, more recent research suggests that opioid agonist may suppress natural killer (NK) cells or interfere with immune response, potentially resulting in an increased incidence of cancer or a reduction in positive outcomes [11].

The pharmacological treatment of opiate dependence is largely centered on the use of long acting opiate agonists such as methadone and buprenorphine. As per illicit opiates, the risk of cancer mortality remains elevated in patients in methadone...
maintenance treatment [15], with particularly high rates of lung, liver and anogenital cancer [18]. Conversely, however, reduced rates of melanoma, cancer of the colorectum, breast, prostate, brain and central nervous system and thyroid have also been observed [6, 14, 18]. Cancer related morbidity and mortality in patients in buprenorphine treatment has yet to be examined.

One alternative to the use of long acting opiate agonists has been the use of opiate antagonists such as naltrexone. Naltrexone has gained popularity over the last decade with the development of a number of sustained released naltrexone preparations, removing the need for daily dosing and problems that arose from the once daily formulation [1]. Cancer have yet to be examined in cohort of patients treated with naltrexone for opiate dependent, however in vitro and in animal models, naltrexone has been found to have both inhibitory and stimulatory effects on the development of cancer, dependent on length of receptor blockage, the dose and the type of cancer involved [10, 20].

The aims of the present study are to investigate the incidence of cancer, and cancer mortality in opiate dependent patients treated with methadone, bu- prenorphine or implant naltrexone and compare them to the general population.

2. Methods

2.1. Sample

Patients who commenced on methadone, bu- prenorphine (both Subutex ® and Suboxone ®) or implant naltrexone (the O’Neil Long Acting Naltrex- one Implant) for the first time between January 2001 and December 2010 in Western Australia (WA) were eligible for inclusion in the study. Methadone or bu- prenorphine patients were identified using the Moni- toring of Drugs of Dependence System (MODDS), while implant naltrexone patients were obtained from an alcohol and other drug clinic, who were the sole providers of implant naltrexone in WA during this period. For ease of calculation, methadone and bu- prenorphine patients were identified using the Moni- toring of Drugs of Dependence System (MODDS), while implant naltrexone patients were obtained from an alcohol and other drug clinic, who were the sole providers of implant naltrexone in WA during their period. To be eligible methadone and buprenorphine patients were required to receive an average of at least 20mg/day of metha- done or 2mg/day of buprenorphine for a minimum of 2 months. For naltrexone implant patients, after a single implant treatment the period of exposure used was 182 days, as per pharmacokinetic data [9, 12]. To be included in the study, patients also required to have at least 60 days of follow up available and be aged 18 to 65 at the first treatment. Additionally patients were excluded if they commenced on two initial treatments in the same month.

A cohort of sex and age matched (5 year age bracket) individuals were selected by the Data Link- age Unit at random from the WA Electoral Roll to act as control group at a ratio of 1:1. Start dates for controls were assigned based as per their corresponding matched case (n = 5137).

2.2. Data

Participant information was linked with the WA Cancer Registry. The WA Cancer Registry contains a list of all patients diagnosed with cancer in WA from 1982 onwards (cancer is a notifiable disease in WA). Participant information was also linked with the WA Death Registry to confirm the cancer relate mortalities identified in the Cancer Registry and pro- vide accurate periods of follow up for each patient. Cross-matching of the data was conducted by the WA Data Linkage Unit using probabilistic matching and extensive clerical review. Treatment data, cancer data and mortality data was available up to the 31st of De- cember 2012. All data provided to the research team was deidentified.

2.3. Data analysis

Analysis of cancer incidence was conducted using two different approaches. Initially the three phar- macotherapies were combined together and compared against the control cohort. Censoring occurred when a patient died (as ascertained via state mortality data) or at the 31st of December 2012. Where possible, a shared frailty model was used to take into account the matched pairs. In the second approach, opiate de- pendent patients were classified based on their initial treatment and were censored when they moved onto a new treatment, died or at 31st of December 2012. In each approach, Kaplan-Meier survival curves were produced and multivariable analysis was performed using Cox proportional hazard regression to examine the effect treatment type. In the first ap- proach, only the variable ‘history of cancer’ was considered in the analysis as both age and sex had be matched in the two groups. In the second approach, all three variables were taken into consideration (his- tory or history of cancer, age and sex).

Univariate cox regression was used to compare
incidence of site specific incidence of cancer, with cancer divided into 14 categories: Lip, oral cavity and pharynx (ICD-10: C00 - 14), digestive organs (C15 - 26), respiratory organs (C45 - 49), breast (C50), female genital organs (C51 - 58), male genital organs (C60 - 63), urinary tract (C64 - 68), eye, brain and central nervous system (CNS) (C69 - 72), thyroid (C73 - 75), lymphoid (C81 - 96) and Ill-defined (C76 - 80).

Univariate analysis was also used to compare survival rates in patients diagnosed with cancer. A univariate approach was used because of the low number of cases in each category. Time commenced from the date of cancer diagnosis and was censored at death or the 31st of December 2012. Survival rates were analyzed only for all types of cancer, rather than type specific cancer mortality due to the low incidence of most types of cancer.

2.4 Ethics

This study protocol was reviewed and approved by the Department of Health Human Research Ethics Committee (2012/63). Reciprocal approval was granted by the University of WA Human Research Ethics Committee (RA/4/1/1864).

3. Results

3.1. Demographics

Participants were predominantly male (66.1%) and in their early 30’s commencement of study follow up. Participants were followed up for an average of 7.3 years, with followed up on their initial treatment for an average of 5.4 years. The average time on treatment was shorter for naltrexone than for both methadone and buprenorphine. History of cancer and rate of cancer in the 5 years leading up to treatment were similar across the treatments (Table 1).

3.2. Rates of cancer

Rates of cancer in opiate dependent patients following treatment induction was lower than non-dependent controls (HR 0.69, CI: 0.47 – 1.00, p=0.05) (Figure 1). Incidences of cancer in methadone (HR 0.81, CI: 0.49 - 1.34, p = 0.42), buprenorphine (HR 0.74, CI: 0.41 - 1.33, p = 0.31) and naltrexone (HR 0.65, CI: 0.28 – 1.50, p=0.31) participants were all lower, but were not statistically significantly different to the control cohort. Increasing age of treatment commencement was associated with an increased cancer incidence (HR 1.11, CI: 1.09 – 1.13, p < 0.01), while rates of cancer in females were increased but not significantly different to male patients (HR 1.45, CI: 0.98 – 2.15, p = 0.06). History of cancer was not significantly associated with cancer incidence (p=0.61).

3.3. Types of cancer

Site/type specific rates of cancer did not vary significantly between all treated opiate dependent patients and the control patients (Table 2). However, within patients treated with methadone and naltrexone treated patients high rates of respiratory cancer were observed (HR 7.53, CI: 1.46 – 38.93, p = 0.02 and HR 7.65, CI: 1.07 – 54.48, p = 0.04 respectively). Conversely, no incidence of respiratory cancer were observed in buprenorphine patients. The only type of respiratory cancer observed in the study was cancer of the bronchus and lung.

Table 1: Demographics and treatment information for opiate dependent patients treated with methadone, buprenorphine or naltrexone patients (first treatment), all treated patients and a cohort of controls.

<table>
<thead>
<tr>
<th></th>
<th>Methadone (n=2,227)</th>
<th>Buprenorphine (n=1,952)</th>
<th>Naltrexone (n=958)</th>
<th>Any treatment (n=5,137)</th>
<th>Control (n=5,137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>67.1</td>
<td>65.4</td>
<td>64.7</td>
<td>66.0</td>
<td>66.0</td>
</tr>
<tr>
<td>Average age (year ± sd) of 1st treatment</td>
<td>32.1 ± 8.3</td>
<td>31.7 ± 8.1</td>
<td>30.9 ± 8.3</td>
<td>31.8 ± 8.3</td>
<td>31.7 ± 8.4</td>
</tr>
<tr>
<td>Average time spent on treatment (years)(range)</td>
<td>2.6 (0.2 – 12.0)</td>
<td>2.2 (0.2 – 11.4)</td>
<td>0.9 (0.2 – 6.2)</td>
<td>3.2 (0.2 – 12.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Average dose ± sd (mg)</td>
<td>54.3 ± 23.8</td>
<td>14.7 ± 7.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Average follow up (years)</td>
<td>5.8 ± 3.3</td>
<td>4.8 ± 3.4</td>
<td>5.3 ± 3.5</td>
<td>7.3 ± 3.0</td>
<td>7.5 ± 2.9</td>
</tr>
<tr>
<td>History of cancer</td>
<td>0.5% (11)</td>
<td>0.5% (9)</td>
<td>0.6% (6)</td>
<td>0.5% (26)</td>
<td>0.7% (35)</td>
</tr>
<tr>
<td>Cancer 5 years pre-treatment</td>
<td>0.3% (7)</td>
<td>0.2% (3)</td>
<td>0.1% (1)</td>
<td>0.2% (11)</td>
<td>0.4% (19)</td>
</tr>
</tbody>
</table>
Figure 1. Kaplan-Meier curves for time to cancer diagnosis in opiate dependent patients treated with methadone, buprenorphine and/or implant naltrexone compared with a cohort of randomly selected controls.

Figure 2. Kaplan-Meier five year survival curve for methadone, buprenorphine, naltrexone and control patients diagnosed with cancer, from time of diagnosis to death (cancer related fatalities).
3.4. Cancer survival

For those diagnosed with cancer, mortality was elevated in treated opiate dependent patients (HR 2.68, CI: 1.03 – 6.97, p = 0.04) compared with the controls. Mortality rates were significantly elevated in patients treated with methadone (HR 3.19, CI: 1.07 – 9.53, p = 0.04), while both buprenorphine (HR 3.07, CI: 0.78 – 12.15, p = 0.11) and naltrexone (HR 3.73, CI: 0.77 – 18.02, p = 0.10) were not significantly different to the controls (Figure 2).

4. Discussion

4.1. Rates of cancer

Interestingly none of the three opiate pharmacotherapies were associated with an increased risk of cancer, regardless of the increased prevalence of known risk factors generally associated with opiate dependent patients (blood-borne and sexually transmitted diseases, heavy consumption of alcohol and tobacco, low socio-economic status) [7, 13, 19]. Surprisingly, treated opiate dependent patients tended towards a reduction in the incidence of cancer. While the results were unexpected, they were congruent with a similar study of cancer morbidity examining rates of cancer in patients treated with methadone in Israel, where they also found no significant difference in standardized incident ratios in methadone patients as compared with the general population [6]. With the exception of this paper, the majority of previous studies examining cancer in opiate dependent patients have focused on cancer related mortality rather than morbidity.

While this is the first study to examine incidence of cancer in patients treated with implant naltrexone, non-clinical cancer studies of naltrexone date back to the 1980’s. In animal models the use of single daily doses of low doses of naltrexone, resulting in small periods of receptor blockade has been shown to reduce the incidence and growth of tumors [20]. By repeatedly blocking the opioid receptors for short period of time, it is believed that the opioid system is up-regulated, increasing levels of meta-encephalin which restrict the growth of cancer cells and increase NK cell activity and T cell function [4]. This work has led to the development of low dose naltrexone (LDN) protocols for the treatment of cancer in humans. In comparison, it is likely that implant naltrexone provides continuous receptor blockade for around 6 months and then partial blockade for another 6 months. The combination of both continual and intermittent receptor blockade may extinguish any effect that ei-

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Table 2: Rates of cancer in opiate dependent persons (and the number) treated with methadone, buprenorphine or implant naltrexone compared with non-dependent controls, expressed per 10 000 patient years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Methadone (n=2,227)</th>
<th>Buprenorphine (n = 1,954)</th>
<th>Naltrexone (n= 958)</th>
<th>Any Rx (n=5,139)</th>
<th>Control (n=5,139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of cancer</td>
<td>15.6 (20)</td>
<td>13.8 (13)</td>
<td>11.9 (6)</td>
<td>12.0 (45)</td>
<td>17.5 (67)</td>
</tr>
<tr>
<td>Survival rates (%)</td>
<td>70.0 (14)**</td>
<td>84.6 (11)</td>
<td>66.7 (4)**</td>
<td>75.6 (34)**</td>
<td>89.6 (60)</td>
</tr>
<tr>
<td>Lip, oral cavity and pharynx</td>
<td>1.6 (2)</td>
<td>3.2 (3)</td>
<td>5.9 (3)</td>
<td>2.7 (10)</td>
<td>4.4 (17)</td>
</tr>
<tr>
<td>Digestive Organs</td>
<td>0.8 (1)</td>
<td>3.2 (3)</td>
<td>-</td>
<td>1.1 (4)</td>
<td>1.0 (4)</td>
</tr>
<tr>
<td>Respiratory Organs</td>
<td>3.9 (5)**</td>
<td>-</td>
<td>4.0 (2)**</td>
<td>1.9 (7)</td>
<td>0.5 (2)</td>
</tr>
<tr>
<td>Bone and cartilage</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melanoma and skin</td>
<td>4.7 (6)</td>
<td>3.2 (3)</td>
<td>-</td>
<td>2.4 (9)</td>
<td>4.7 (18)</td>
</tr>
<tr>
<td>Mesothelial and soft tissue</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.3 (1)</td>
<td>0.8 (3)</td>
</tr>
<tr>
<td>Breast1</td>
<td>4.8 (2)</td>
<td>3.1 (1)</td>
<td>-</td>
<td>3.1 (4)</td>
<td>4.6 (6)</td>
</tr>
<tr>
<td>Female genital organs1</td>
<td>4.8 (2)</td>
<td>3.1 (1)</td>
<td>-</td>
<td>3.1 (4)</td>
<td>2.3 (3)</td>
</tr>
<tr>
<td>Male genital organs2</td>
<td>1.2 (1)</td>
<td>-</td>
<td>-</td>
<td>0.4 (1)</td>
<td>1.2 (3)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.3 (1)</td>
</tr>
<tr>
<td>Eye, brain and CNS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ill-defined</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>0.8 (1)</td>
<td>2.1 (2)</td>
<td>-</td>
<td>1.1 (4)</td>
<td>2.1 (8)</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01  1=Rates for female patients  2=Rates for male patients
4.2 Types of cancer

Rates of respiratory cancer, comprised solely of bronchus and lung cancer were elevated in the methadone and naltrexone cohort as compared with the controls. Such finds are not unexpected given the high rates of cigarette smoking in opiate dependent patients [7] and the strong correlation between lung cancer and cigarette smoking [3]. Surprisingly, however no incidence of bronchus, lung or any type of respiratory cancer was observed in patients treated with buprenorphine. The absence of lung cancer in the buprenorphine cohort may be a result of the relatively small size of the cohort, reduced levels of risk factors in the cohort (lower levels of smoking) or possibly as a protective effect of the buprenorphine itself.

4.3 Cancer survival

Survival rates were significantly poorer in opiate dependent patients who had received treatment, with patients dying at more than 2.5 times the rate of the controls. Similarly survival rates in patients diagnosed with methadone were significantly poorer than for the controls, with methadone patients diagnosed with cancer dying at more than three times the rate of the controls. Survival in buprenorphine and naltrexone patients were not significantly different from the control population, however crude rates all appear to be somewhat elevated with mortality rates of 15.3% and 33.3% respectively, compared with the controls at 10.4%. The lack of significance may be the result of the low incidence of cancer.

Several explanations can be hypothesized to explain poorer survival in opiate dependent patients in treatment. One explanation maybe that the types of cancer found in these patients has poorer prognoses, as seen in the high incidence of lung cancer and associated high rates of mortality in methadone patients. Alternatively, the lifestyle of these patients may mean they are more likely to be diagnosed at a later stage, have difficulty complying with treatment given or have additional risk factors for poor outcomes.

Strengths and limitations

Given the relatively low incidence of cancer, the sample size utilized in this study was a significant limitation, restricting the power at which comparisons between the four groups could be made especially in terms of specific types of cancer. Additionally, the study utilized state health data and thus only cancer diagnosis and fatalities occurring outside of WA may not have been captured.

As per most epidemiological studies, the potential presence of confounding variable poses a significant limitation to the study. For example, patient on naltrexone may represent the more motivated patients or patients with less severe addiction, who wish to stop using opiates rather than be managed on a maintenance treatment. Such may be indicative of a shorter period of dependence/opiate exposure, a strong support system, higher socio-economic status etc. Given the high rates of lung cancer, the inability to control for smoking status is a major limitation. Unfortunately only minimal demographic and no drug use history variables were available to assist in controlling for such potential confounders.

This study is the first to examine rates of cancer in opiate dependent patients treated with buprenorphine and naltrexone and combines both cancer diagnoses and cancer mortality. The data represented is inclusive of all patients treated between January 2001 and December 2011 and uses routinely collected data on a reportable disease. Thus the results are a good indicator of actual rates of cancer and cancer related mortality.

5. Conclusions

The use of opiate pharmacotherapies in the treatment of opiate dependence were not associated with an increased incidence of cancer, however survival rates appeared to be elevated.

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and enhancement of natural killer cell activity by methionine-enkephalin Brain Behav Immun. 2: 114 - 122.

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Role of the funding source
The State Health Research Advisory Council was not involved in the study design, collection, analysis and interpretation of data, the writing of the report or the decision to submit the article for publication.

Contributors
EK was responsible for obtaining ethics approval, study design, obtaining the data, data analysis and drafting of the manuscript. TD oversaw the data analysis and presentation of results. GH supervised EK and oversaw the study. GH contributed to the drafting of the manuscript.

Conflict of interest
None

Ethics
Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. Participant did not provide informed consent to participate in this study. A waiver of consent was granted by the Human Research Ethics Committee as the study met the requirements for a waiver of consent as set out in the National Statement on Ethical Conduct in Human Research (2007).
DEAL WITH THE PRESENT, JUMP START THE FUTURE