Psychiatric Comorbidities in Opioid-Dependent Patients: Influence upon Methadone Dosage

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Author disclosure

Statement of Potential Conflicts of Interest, September 2015

Relating to this presentation, the following relationships could be perceived as potential conflict of interests:

Carlos Roncero has received fees to give lectures for Janssen-Cilag, Ferrer-Brainfarma, Pfizer, Reckitt Benckiser/Indivior, Lundbeck, Otsuka, Servier, Lilly, GSK, Rovi and Astra. He has received financial compensation for his participation as a member of the Janssen-Cilag, Lilly, and the Shire board. He has carried out the PROTEUS project, which was funded by a grant from Reckitt-Benckisert/Indivior.
ADDICTION AND DUAL DIAGNOSIS UNIT
VALL HEBRON
Dual Diagnosis & Opiate Dependence

Epidemiology.

Clinical Relevance.

Dual Diagnosis and Methadone Treatment.
149 regular heroin users aged between 18-30 and resident of Barcelona, Spain. 33% were women, average age 25.1 years. Psychiatric evaluation was carried out with the Psychiatric Research Interview for Substance and Mental Disorders (PRISM). 71% cocaine-dependents. 32% of the sample had never been treated for substance use.

67.1% had at least one lifetime psychiatric comorbidity, antisocial personality and mood disorders being the most frequent conditions (33% and 26%).

Mood, anxiety and eating disorders were more common among women than men.
OPIATE USE AND DUAL DIAGNOSIS

288 young-adult cocaine and/or heroin users (aged 18–30) recruited in nonclinical settings. 158 were reinterviewed 18 months later using the Psychiatric Research Interview for Substance and Mental Disorders. By the time of the follow-up, 18% of subjects had acquired at least one additional SUD and nearly 11% another non-SUD Axis I disorder.

Female subjects, as well as those with lower frequency of substance use at baseline, first use of heroin at a younger age and worsening SUDs were associated with a greater likelihood of developing a new Axis I disorder.
Prevalence of psychiatric disorders among heroin users who received methadone maintenance therapy in Taiwan.

Fan CY, Tan HK, Chien IC, Chou SY.

Abstract

BACKGROUND: Many patients under methadone maintenance treatment are present with comorbid psychiatric symptoms.

OBJECTIVE: We wish to examine the prevalence of psychiatric disorders among heroin users who received methadone maintenance therapy (MMT) in Taiwan.

METHODS: By combining the National Health Insurance Research database and Center for Disease Control database, 18,271 heroin users who received MMT were defined as the subject group and after matching age and sex, 73,084 patients were randomly selected as the control group.

RESULTS: The 1 year prevalence of any psychiatric disorder, any psychotic disorder, neurotic and other nonpsychotic disorder among MMT patients and control group were 13.14% versus 2.50% (OR 5.89, CI 5.53-6.27), 4.21% versus 1.29% (OR 3.38, CI 3.07-3.72), and 9.89% versus 1.31% (OR 8.25, CI 7.62-8.94), respectively.

CONCLUSION: The prevalence of any co-morbid psychiatric disorder among MMT patients is almost six times higher than the control group.

SCIENTIFIC SIGNIFICANCE: A thorough psychiatric screening and appropriate aggressive intervention should be incorporated into an effective methadone treatment program.
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The PROTEUS Study

Primary Objective

• To describe the current therapeutic management of opiate-dependent patients included in a replacement therapy program in care centers for opiate-dependent patients.

• N=624 from 74 centers.

Regular article
Heroin Addict Relat Clin Probl 2011; 13(3): 5-16

Therapeutic management and comorbidities in opiate-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study

Carlos Roncero¹,², Gideon Fuste¹, Carmen Barral¹, Laia Rodríguez-Cintas¹, Nieves Martínez-Luna¹, Francisco José Eiroa-Orosa²,³, Miguel Casas²,³ on behalf of the PROTEUS study investigators

¹ Outpatient Drug Clinic, Department of Psychiatry, Vall d’Hebron University Hospital, Barcelona. Public Health Agency Barcelona (ASPB), Spain, EU
² Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, EU
³ Department of Psychiatry, Vall d’Hebron University Hospital, Barcelona, Spain, EU
The PROTEUS study

• We carried out an observational, cross-sectional, multicenter study from September 2008 to February 2009.

• Patients > 18 years, with written informed consent (in accordance with the Declaration of Helsinki), with a diagnosis of opiate dependence according to DSM-IV-TR criteria and currently scheduled in a replacement therapy program in Spain.
The PROTEUS Study

-Selection criteria

• Patients of both sexes, aged ≥18 years.
• Patients diagnosed with opiate dependence, according to DSM-IV TR diagnostic criteria.
• Patients currently undergoing a rehabilitation therapy program in care centers for opiate-dependent patients.
• Patients who gave written informed consent to participate in the study.
The PROTEUS Study

- The most frequent replacement therapy was methadone (94%), usually in \(< 40 \text{ mg/day (38\%)}\)
- 40-80 mg/day doses (40\%)
- > 80 mg/day doses (22\%)
- Average follow-up period: 45.88 months (x=25 months).

Roncero et al, 2011
Psychiatric comorbidities were clinically detected in 68% of all evaluable patients.

The most frequent disorders were:
- Anxiety (53%)
- Mood (48%)
- Sleep (41%)

Drug-related disorders were found in 36% of patients.
**Axis I & II Disorders**

Psychiatric comorbidities were analyzed according to their DSM-IV-TR axis. For this purpose, psychiatric comorbidities were classified as follows:

- **AXIS I**: schizophrenia and other psychotic disorders; mood, anxiety, somatoform, factitious, dissociative, eating and adaptive disorders.
- **AXIS II**: personality disorders

52% of patients had at least one comorbidity on Axis I; usually one (48%) or two (41%). Among them, 15% had schizophrenia and other psychotic disorders, and 64% had mood disorders. Comorbidities on Axis II were found in 19% of patients.

No significant differences were found in the proportion of patients with Axis II comorbidities according to the presence of Axis I comorbidities (p>0.05).
Dual Diagnosis & Opiate Dependence

We assess the psychiatric comorbidities of a large OD population enrolled in OAT programs we compare the different socio demographic and clinical characteristics according to whether or not they had Dual Diagnosis.

The EuropASI was used to assess the dependence severity and related problems, in a face-to-face interview conducted by a trained interviewer.

In addition, mood and psychotic disorders were analyzed according to patient’s perception and doctor’s clinical perception.

A patient was considered to suffer mood disorders if the EuropASI section I patient’s items 3 (Experienced serious depression), 9 (Experienced serious thoughts of suicide) and 10 (Attempted suicide), and interviewer’s items 14 (Obviously depressed/withdrawn) and 19 (Having suicidal thoughts) were marked in the clinical report form (CRF).

A patient was considered to suffer psychotic disorders if the patient’s item 6 (Experienced hallucinations) and the interviewer’s item 17 (Having trouble with reality testing, thought disorders, paranoid thinking) were marked.

(Roncero et al, submitted)
As with the case of affective disorders, patient and doctor opinion frequently coincided.

The same was found regarding the presence of psychotic disorders in 33% of cases; only 3% of the time did doctors clinically detect psychotic disorders in contrary to the patient’s opinion (p<0.0001).

When analyzed by methadone treatment with or without cocaine, patients treated concomitantly for cocaine abuse were found to have had significantly more psychotic disorders in the last month (6% versus 1%; p=0.0004). No other significant differences were found.

The most relevant affective and psychotic disorders were suicide attempts and hallucinations.

One percent of patients had attempted suicide in the last month, with a mean of 0.67±0.58 attempts per patient.

The proportion of patients attempting suicide throughout their life was 22%, with a mean of 2.28±1.79 attempts.

As for hallucinations, they were experienced by 2% of patients in the last month, and by 27% of patients throughout their life.
The prevalence of psychiatric comorbidities in OD patients receiving OAT in Spain is extremely high, at 68%.

These dual patients displayed more comorbidities, lower employment status and greater severity of a multitude of medical and social problems than did non-dual patients.

Physicians treating OD patients should be aware of these facts in order to treat this specific condition comprehensively.

Roncero et al (submitted)
Dual Diagnosis & Opiate Dependence

Epidemiology.

Clinical Relevance.

Dual Diagnosis and Methadone Treatment.
Psychopathology and drug use in dual opiate-dependent patients.

n=150 dual bipolar
Naltrexone implant (n = 317), methadone (n = 521)

Nearly 32% had at least one psychiatric comorbidity.

DD patients generally had significantly greater odds of drug-related hospitalization pre-treatment compared with their non-DD counterparts.

Treatment of persons without depression, anxiety, or personality disorder with naltrexone implant was associated with increased risk of 'non-opioid' drug-related hospitalization, while methadone treatment was associated with increased risk of 'opioid' drug-related hospitalization.
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• 129 heroin addicts who also met the criteria for treatment resistance, 66 with one or more DSM-IV axis I psychiatric diagnosis (DD patients), and 63 without DSM-IV Axis I psychiatric comorbidity (NDD patients) were monitored prospectively (6 years on average, min. 1, max. 9) during a methadone maintenance treatment program (MMTP).

• The rates for survival-in-treatment were about 50% for NDD patients and about 70% for DD patients.

• Contrary to expectations, treatment-resistant patients with psychiatric comorbidity showed a better long-term outcome than treatment-resistant patients without psychiatric comorbidity.
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Contrary to expectations, treatment-resistant patients with psychiatric comorbidity showed a better long-term outcome than treatment-resistant patients without psychiatric comorbidity.
Heroin-dependent patients with psychiatric comorbidities may benefit from opioid agonist treatment not only because it targets their addictive problem but also, for precisely this reason, it is effective against their particular mental disorder.
Psychiatric comorbidities were detected in 68% of patients (anxiety 53%, mood disorders 48%, sleep disorders 41%, substance-related disorders 36%, personality disorders 27%, etc).

Dual-pathology patients tended to be significantly older (p=0.007) and more frequent users of benzodiazepines (p≤0.0001) and cannabis (p=0.046).

DD patients showed more frequent infectious and non-infectious comorbidities (p≤0.0001), as well as lower employment status (p≤0.0001), lower percentage of drivers (≤0.0001) and higher levels of severity regarding medical (p≤0.0001), employment (p=0.010), alcohol (p≤0.0001), legal (p=0.009), family (p≤0.0001) and psychological issues (p≤0.0001) than non-dual patients.

Roncero et al (submitted)
Dual Diagnosis & Opiate Dependence

Epidemiology.

Clinical Relevance.

Dual Diagnosis and Methadone Treatment.
90 opioid-dependent subjects, 38 with one or more additional Axis I diagnosis.

- There were significant differences between these two groups regarding the methadone dose required for clinical stabilization.

- Dual Diagnosis patients required an average stabilization dose of 154 +/- 84 mg/day of methadone compared to 99 +/- 49 mg/day for patients whose only Axis I diagnosis was Opioid Dependence.

- In the 990-day period considered there were no differences between the two groups of patients in terms of retention in treatment.
78 patients, predominantly men (75.6%), with an average age of 34 yo [22-57] were included.

Both groups with methadone posology ≤ 130 mg/d (n=44) versus methadone posology >130 mg/d (n=34) were similar in term of demographic characteristics, drug consumption and associated treatments.

The presence of psychiatric comorbidities was significantly associated with high-dose methadone (threshold 130 mg/d) [OR 4.6 IC 95% (1.412;14.925)].
Patients requiring high doses of methadone are polydrug addicts.

Patients with psychiatric comorbidities need significant increases in their daily methadone dosage.

Eiden et al, 2012
Dual Diagnosis & Opiate Dependence

The dose of the agonist drug might have to be increased in patients with comorbid psychiatric disorders.

• OD patients with bipolar I disorder needed a higher methadone dosage in the stabilization phase, although this difference was not statistically significant. Maremmani AG, Rovai L, Bacciardi S, et al. The long-term outcomes of heroin dependent-treatment-resistant patients with bipolar 1 comorbidity after admission to enhanced methadone maintenance. J Affect Disord. 2013;151(2):582-9.

• It has been reported that higher dosages of methadone may be beneficial for a decrease in Axis-I comorbidity Herrero MJ, Domingo-Salvany A, Brugal MT, et al. Incidence of psychopathology in a cohort of young heroin and/or cocaine users. J Subst Abuse Treat. 2011;41(1):55-63.
The dose of the agonist drug might have to be increased in patients with comorbid psychiatric disorders.

• Negative correlations were found between PTSD spectrum severity and methadone dose \((r=0.225; \ p=0.042)\) Dell’Osso L, Rugani F, Maremmani AG, Bertoni S, Pani PP, Maremmani I. Towards a unitary perspective between post-traumatic stress disorder and substance use disorder. Heroin use disorder as case study. Compr Psychiatry. 2014;55(5):1244-51.
The only group associated with leaving an OAT program was the personality disorder group, these disorders being more frequent among patients who had left previous OAT programs than among those who had stayed (46% versus 26%, p=0.0175).

The proportion of patients with at least one psychiatric comorbidity increased significantly by methadone dosage (p=0.0066).

The substance-related disorder group had much to do with this as this particular psychiatric comorbidity was the only one that increased in severity in accordance to methadone dosage (p=0.0109).

Roncero et al (submitted)
<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;40</th>
<th>40-80</th>
<th>&gt;80</th>
<th>p-value*</th>
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<td>Substance-related disorders</td>
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<td>Schizophrenia and other psychotic disorders</td>
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<td>Mood disorders</td>
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<td>Anxiety disorders</td>
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<td>Sleep disorders</td>
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<td>68 (42.8%)</td>
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*p-Value for Chi-Squared test
### Dual Diagnosis & Opiate dependence

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*Chi-Squared test
Dual Diagnosis & Methadone

Diagram:
- Dual Diagnosis
- High Methadone dose

Relationship:
- Dual Diagnosis leads to High Methadone dose
- High Methadone dose influences Dual Diagnosis
Dual Diagnosis & Methadone

Dual Diagnosis

Adherence Compliance?

Psychopatology treatment??

Other

High Methadone dose
Dual Diagnosis & Methadone

Adherence Compliance?

Psychopathology treatment??

Other

High Methadone dose
CONCLUSIONS

• There were **high rates of dual diagnosis** among opiate dependence patients.

• The proportion of patients with psychiatric comorbidities and drug-related disorders **increased significantly** at a higher methadone dosage.

• Our study patients with at least one psychiatric comorbidity were treated with larger doses of methadone.

• Patients receiving high doses of methadone should be watched particularly for signs of further Mental Disorders.
CONCLUSIONS

• Gender differences in opiate-dependent patients are relevant.

• Studies on opiate dependence are relatively scarce.

• Biological and psychosocial features should have to take into account.

• Dual diagnosis seems to be different (anxiety and affective disorders are more prevalent in women).

• More studies should be conducted with a higher number of women.
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Dual Diagnosis & Opiate Dependence

• Why study dual pathology?

• Previous evidence.