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Dose Determination in Dual Diagnosed Heroin Addicts during Methadone Treatment

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Summary

Ninety-nine consecutive responders to treatment for heroin addiction (54 with one or more Axis I psychiatric diagnosis (DD-patients), and 45 without psychiatric comorbidity (NDD-patients), were monitored prospectively (20 months on average, min.1, max. 51), in order to achieve some useful clinical information pertaining to effective methadone dose determination for double diagnosed heroin addicts. First day and first month dosages do not differ between the two groups. Stabilization dosages are higher in DD patients than in NDD patients. The time to reach stabilization phase is longer in DD patients than in NDD patients. Tapering of methadone follows a similar trend in both groups. DD patients need more attention from clinicians, especially when stabilization dosage has to be established.

Key Words: Methadone Maintenance; Psychiatric Comorbidity; Methadone Dose Determination

1. Introduction

Methadone is a long-acting opioid analgesic with well-characterized pharmacological properties that make it suitable for the treatment of heroin addicts on a maintenance protocol. The development of methadone maintenance treatment programs (MMTPs) started in New York in the mid-sixties, and since then it became the most widely prescribed treatment for heroin addiction worldwide. In the first study, the initial dose was around 35 milligrams a day, and it was gradually increased to standard doses of approximately 100 mgs/d [1]. However, several decades later, there is not yet complete agreement on the doses of methadone to be prescribed in a maintenance program, and the doses used in randomized clinical trials are often higher than those currently used in routine clinical practice [7]. These differences may explain recurring claims for alleged low methadone effectiveness,

since the response to methadone treatment (in terms of retention into therapy, negative urinalysis for illicit drugs, and socialization) is dose-dependent.

An outpatient treatment service for drug addicts (Dual Diagnosis Unit) has been established many years at the "Santa Chiara" University Hospital, Department of Psychiatry, University of Pisa, Italy, EU.

The service was initiated with the aim to treat drug abusers, in particular heroin addicts, with a double diagnosis; that is, subjects with one or more DSM-IV-TR Axis I psychiatric diagnoses in addition to that of Opioid Dependence. In order to assess the existence of possible peculiarities in the treatment protocols used in these patients, an equal number of heroin addicts with no additional Axis I mental disorders were enrolled in the program. Some recent publications report the main outcomes of this study and show that, when a proper stabilization level is attained in the long-term, du-

ally diagnosed opioid dependent patients who survive early attrition tend to stay in treatment longer than those without psychiatric co-morbidity [3, 6]. Retention in the program is one of the hard-core endpoints that validates treatment for heroin addiction.

The aim of this study was that of describing and discussing in detail the differences observed between the treatment participants in the two groups and stress their relevance in various treatment phases.

2. Methods

2.1 Setting

Since 1993, the Pisa-MMTP has been using a clinical protocol that has the characteristics of a high-threshold treatment facility for opioid addiction focusing on pharmacological maintenance. After patients at the PISA-MMTP have been safely inducted into treatment with methadone, their doses are gradually increased until the point is reached where there is no more than one urine drug screen which is positive for illicit opiates, cocaine, or benzodiazepines in the previous sixty-day's period. Once this requirement is fulfilled, the patient is defined as "stabilized" and the maintenance dose reached is referred to as the "stabilization dose". No upper limit for dosage exists. Nevertheless, a time limit has been imposed in this setting: patients who cannot achieve stabilization within one year stop the program and are transferred to local treatment units. The dosage is increased on the basis of the results of urinalyses, and other criteria such as improvement in social parameters does not effect dose stability as long as urine samples stay positive for opiates. Patients are not allowed to raise or lower their doses by themselves. Take-home doses, for at most a 7-day period are allowed, once patients have shown complete compliance with the rules of the programme. Urine samples for analyses are collected randomly almost once a month, to evaluate the metabolites of illicit drugs and benzodiazepines.

2.1 Sample

The sample included in this study consisted of 99 consecutive stabilized patients followed during treatment for an average of 592 ± 417 days (min 365 max 1536). During the follow-up period we excluded patients with a negative outcome. We considered a "negative outcome" when a patient has failed to achieve "stabilization" within a year (see above) or has relapsed into addictive behaviour after a period of stabilization. We are aware that this limit precludes an intention to treat analysis. On the other hand, we are forced to operate within a rigid number of slots.

Most of the patients were male ($n=76$; 76.8%), single ($n=69$; 69.7%) and unemployed ($n=58$; 59.8%), and had less than 13 years of formal education ($n=67$; 69.8%). Age ranged

between 19 and 46 years (mean = 30 sd 6). The age of the first use was 18 ± 4 (min 13 max 31). The age of the continued use was 20 ± 4 (min 14 max 31). The mean duration of drug addiction was 8.6 years (sd 5.9 (min 1 month max 22 yrs)). The age of the first therapeutic contact was 27 ± 6 (min 16 max 45). 85 (85.9%) patients showed physical complications, 92 (92.9%) had an abnormal mental status at treatment entry. Social adjustment was problematic in 60 (60.9%) patients regarding their family life; 66 (66.7%) regarding their job, 29 (29.3) regarding their romantic involvement and in 57 (57.6%) regarding their social contacts and or their leisure time activities. 53 (53.5%) had legal problems, 68 (68.7%) were polyabusers, 88 (88.9%) had been unsuccessfully treated in the past.

Forty-five subjects had one or more DSM-IV-TR Axis I psychiatric diagnoses in addition to Opioid Dependence and are defined as Dual Diagnosed Patients (or "DD-patients"). Fifty-four subjects did not have any additional Axis I mental disorder diagnosed, and are defined as not having a Dual Diagnosis (or "NDD-patients").

Heroin Addicts with and without Dual Diagnosis do not differ with regard to physical complications, abnormal mental status at study entry, social adjustment (family, job, romantic involvement, social/leisure and legal problems), polyabuse, unsuccessful treatments in the past, age of first use and age of continuous use.

Subjects with psychiatric comorbidity (DD-patients) showed significant differences (after Buonferroni's correction) regarding the duration of addiction, which is less than that reported by N-DD patients (Mean Rank: NDD=58.22 Vs DD=38.80 Mann-Whitney z test= -3.36 p=.0008). According to the literature DD patients are seeking for help earlier (NDD=28±7 yrs Vs DD=25±5 yrs T-test=-2.68 p=0.009).

All patients gave their written informed consent to the study after the procedure had been fully explained.

2.3 Assessment

The following instruments were used to collect data on the variables to be studied:

2.3.1 Drug Addiction History Rating Scale (DAH-RS)

The DAH-RS, (administered at the beginning of treatment) [4] is a multi-scale questionnaire comprising the following categories: sociodemographic information, physical health, mental health, substance abuse, treatment history, social adjustment and environmental factors. The questionnaire rates 10 items: physical problems, mental problems, substance abuse, previous treatment, associated treatments, employment status, family situation, sexual problems, socialization and leisure time, legal problems. (The specific clinical variables addressed are: hepatic, vascular, haemolympathic, gastrointestinal, sexual, dental pathology, HIV

serum status; memory disorders, anxiety disorders, mood disorders, aggression, thought disorders, perception disorders, awareness of illness; employment, family, sex, socialization and leisure time, legal problems; use of alcohol, opiates, CNS depressants, CNS stimulants, hallucinogens, phencyclidine, cannabis, inhalants, polysubstance abuse; frequency of drug use, pattern of use, previous treatments; current treatments). Items have been constructed in order to obtain dichotomous answers (yes/no).

2.3.2 Psychiatric Diagnostic Evaluation. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version.

This user-friendly instrument [2] will help clinicians make standardized, reliable, and accurate diagnoses and avoid the common problem of “premature closure”- the premature focus on one diagnostic possibility. Specifically adapted from the research standard for Axis I structured clinical interviewing for use in clinical settings, the SCID-I covers those DSM-IV diagnoses most commonly seen by clinicians and includes the diagnostic criteria for these disorders with corresponding interview questions. The SCID-I is divided into six self-contained modules that can be administered in sequence: mood episodes; psychotic symptoms; psychotic disorders; mood disorders; substance use disorders; and anxiety, adjustment, and other disorders

The criteria for a “dual diagnosis” are satisfied when clearly distinct symptoms of heroin dependence and of an autonomous psychiatric disorder have been identified.

Axis II comorbidity was excluded when our sample was clustered. Axis I and Axis II disorders are two related but separate dimensions of psychopathology. In addition, a wide range of personality disorders are present among substances abusers, so it is very difficult to identify subgroups on the basis of Axis II disorders. In this study the Axis I-diagnosed heroin addict group served as a “psychiatric” control group; the non-Axis I diagnosis group served as a traditional “normal” control group. NDD patients were excluded from this study when an Axis II disorder was present.

2.4 Statistical analysis

We report the dosage of the first day, the weekly dosage for the first month, the every four-month dosage for the entire duration of the study (comparing these dosages between heroin addicts with and without dual diagnosis). We also compared the stabilization dose and the time required to achieve it. We used the routines of SPSS 4.0. The statistical tests were considered significant at the level of $p < 0.05$.

3. Results

Table 1 compares first-day dosages in heroin addicts with

and without dual diagnosis.

The first day mean dosage was 46 ± 37 for NDD-patients and 40 ± 22 for DD-patients respectively. The most frequent dosage (mode) was 30 mg for NDD-patients and 40 for DD-patients respectively. The median (the dose which splits the sample in halves) dose was 37.5 mg for NDD-patients and 40 for DD-patients respectively. One third of the sample was treated with dosages above 40mg. The highest dosages in NDD-patients were 130 mg for one patient and 200 mg for two patients. Those in DD-patients were 80 mg for two patients and 100 mg for two patients. These differences were not statistically significant (Mann-Whitney U - Wilcoxon Rank Sum W Test $z = -0.41$ 2-tailed $p = 0.67$).

Table 2 reports the weekly dosages within the first month. During the first week dosages increased by 139.5%. In the following three weeks dosages increased by 120.0%, 112.5% and 104.9%, respectively. No significant differences were found with the exception of day-7 dosages that were higher in NDD than DD-patients.

Table 3 reports the dosage variation for the first month of treatment in Heroin Addicts with and without dual diagnosis. Only at the end of the first week are variations statistically different according to groups with and without dual diagnosis. No patients with dual diagnosis reduced dosages, but a great percentage of these patients did not increase first day dosage during the first week. No differences between groups have been shown during the second, the third and the fourth week.

Considering the follow-up period, the methadone mean stabilization dosage (highest dose taken for at least 4 weeks, related to “positive outcome”) was 119 ± 70 mg/day (min 22 max 400). The mode and the median were 80 mg/day and 100 mg/day respectively. Seventeen patients (17.2%) were treated with dosages of 60 mg/day or less. Thirty-six patients (35.4%) received a dosage greater than 120 mg/day. DD-patients need a stabilization dosage higher than NDD-patients (136 ± 85 Vs 105 ± 51 ; T-test = 2.12 $p = .03$).

The time to reach the stabilization dose (months) was 5 ± 5 (min 1 max 31). The mode was 3 and the median was 3. Only 7 patients (7.1%) needed a time longer than 9 months. It takes longer to stabilize DD-patients than NDD-patients (7 ± 6 Vs 3 ± 2 ; T-test = 4.34 $p < .001$).

Table 4 displays the trends of dosage over time, separately for DD and NDD-patients, and for the whole sample. Time is divided into four-month intervals, and mean dosages for correspondent intervals are reported. NDD-subjects need higher methadone doses than DD subjects at the beginning of the program (interval 1), but the relationship reverses soon after in interval two, when DD-patients are the ones who require higher dosages. The latter relationship is maintained all through the study period, despite later changes in dose-trend in the single groups. Nevertheless, the course of stabilization appears to be similar in NDD and DD-patients, since both groups show a trend towards an increase of methadone dose in interval 1 and 2, with peak mean-dose reached at the end

Table 1. First day methadone dosage in 99 responders to treatment heroin addicts with and without dual diagnosis at the start of methadone maintenance

Dosage (mg)	Total sample N=99	NDD N=54	DD N=45
	N (%)	N (%)	N (%)
10	7 (7.1)	2 (3.7)	5 (11.1)
15	3 (3.0)	1 (1.9)	2 (4.4)
20	11 (11.1)	7 (13.0)	4 (8.9)
30	25 (25.3)	16 (29.6)	9 (20.0)
35	1 (1.0)	1 (1.9)	
40	19 (19.2)	8 (14.8)	11 (24.4)
45	1 (1.0)	1 (1.9)	
50	11 (11.1)	6 (11.1)	5 (11.1)
60	8 (8.1)	4 (7.4)	4 (8.9)
70	3 (3.0)	2 (3.7)	1 (2.2)
80	4 (4.0)	2 (3.7)	2 (4.4)
90	1 (1.0)	1 (1.9)	
100	2 (2.0)		2 (4.4)
130	1 (1.0)	1 (1.9)	
200	2 (2.0)	2 (3.7)	

Table 2. Weekly dosage for the first month of treatment in heroin addicts with and without dual diagnosis

	Total sample N=99	NDD patients N=54	DD patients N=45
	M±s	M±s	M±s
Day1	43±31	46±37	40±22
Day 7	60±35	66±38*	53±31*
Day 14	72±41	76±40	67±43
Day 21	81±48	85±42	77±54
Day 28	85±49	89±44	80±55

* Mann-Whitney U - Wilcoxon Rank Sum W $p < 0.05$

of interval 2 for both groups. From interval 3 on, a trend towards lowering of dosage is seen, which temporarily inverts in interval 5 for DD-subjects., and in interval 7 for NDD ones. Dose values tend to raise for DD, but not for NDD-patients, as late as at interval 9.

The retention in treatment of patients with and without psychiatric comorbidity is not different, In DD-patients, 93.36% are censored, in comparison with 88.89% of NDD patients. At the start of treatment the attrition sample is similar for the two groups. In the first four months period no NDD-

patients leave the treatment whereas DD-patients show the greatest rate of attrition. After the 8th month of treatment no DD-patient leaves treatment for reasons related to treatment failure. Among NDD patients it is possible to find cases of unsuccessful treatment for as long as twelve months. After this period no NDD-patient leaves the treatment. Leu-Desu Statistics ($F = 1.36$; $p = 0.24$) demonstrates that the retention rates of the two groups are similar.

Table 3. Dosage variation for the first month of treatment in Heroin Addicts with and without dual diagnosis

Methadone dosage variation	Total sample N=99	NDD patients N=54	DD patients N=45	Chi
Day1-Day7 period				
Decreased dosages	3	3 (100)	0 (0)	9.59**
Increased dosages	68	42 (61.8)	26 (38.2)	
No variations	28	9 (32.1)	19 (67.9)	
Day7-Day14 period				
Decreased dosages	5	4 (80.0)	1 (20.0)	1.62
Increased dosages	66	34 (51.5)	32 (48.5)	
No variations	28	16 (57.1)	12 (42.9)	
Day14-Day21 period				
Decreased dosages	3	1 (33.3)	2 (66.7)	0.56
Increased dosages	56	31 (55.4)	25 (44.6)	
No variations	40	22 (55.0)	18 (45.0)	
Day21-Day28 period				
Decreased dosages	3	3 (100)	0 (0)	4.27
Increased dosages	32	20 (62.5)	12 (37.5)	
No variations	64	31 (48.4)	33 (51.6)	

*p<0.01 **p<0.001

Dosages increase, in the two groups, during all periods in a statistically significant way (Mann-Whitney U - Wilcoxon Rank Sum W p<0.01)

Table 4. Four monthly period mean dosage in heroin addicts with and without psychiatric comorbidity

	Total sample		NDD patients		NDD patients	
	N	M±s	N	M±s	N	M±s
1st Quarter	94	89±53	49	91±44	45	87±61
2st Quarter	76	106±70	37	102±53	39	111±83
3st Quarter	66	93±59	31	81±49	35	102±67
4st Quarter	56	81±57	25	70±44	31	90±64
5st Quarter	48	77±57	23	63±41	25	92±66
6st Quarter	42	72±53	21	58±38	21	87±62
7st Quarter	37	69±46	20	60±35	18	77±54
8st Quarter	33	61±37	17	55±30	16	67±43
9st Quarter	20	63±36	10	51±24	10	71±42
10st Quarter	11	69±40	5	50±21	6	84±47

4. Discussion

The first day methadone dosage aims to eliminate the opioid withdrawal syndrome. This dosage is generally comprised between 20 and 40 mg [8]. Although our data demonstrate that 6.1% of our sample need a methadone dose greater than 80 mg. In a few cases this dosage was raised to over 100 mg. Undermedication of a patient can result in a rapid termination from therapy as patients will “escape” and not return for follow up. So it is crucial to have a safe methodology to increase a methadone dosage over 20-40 mg the same day. We give the first 20 mg to the patients and we re-evaluate withdrawal symptoms after 2 hours. If symptoms are still present an additional dose of 20 mg is provided, followed by a 2-hour period of clinical observation. This procedure should be repeated until withdrawal symptoms are extinguished. The dosage so established is the daily dose for the earlier induction phase and must be repeated until a pharmacological steady state is reached (3-4 days). We used the exceptional dosage (200 mg) in two treatment seeking pushers without psychiatric comorbidity. DD-patients do not need a greater first-day dosage than NDD-patients. This trend is maintained throughout the first month of treatment. Summarizing, we can state that there is no difference either in treating withdrawal symptoms or in methadone dosage required during the first month of treatment between patients with and without psychiatric comorbidity.

As we previously demonstrated [3, 5, 6], the stabilization dosage is higher in DD-patients than in NDD-patients. Psychiatric comorbidity does not differently affect the opioid tolerance in DD compared to NDD-patients, as demonstrated by the first day methadone dosage which is required. On the other hand, psychiatric illness influences therapeutic maintenance dose: more methadone is needed in DD-patients to improve their formerly dysfunctional behaviors. On clinical grounds, the presence of psychiatric illness is not to be considered as a drawback when adequate methadone doses have to be administered. On the contrary, undermedicated DD-patients may be mistaken for non-responders to the treatment if the attitude of the treating clinician is to be too limiting with dosages. The time to reach the stabilization dose appears to be longer in our patients than what is frequently reported in the literature (5 months Vs 1 month). This time is longer in DD than in NDD-patients (7 months Vs 3 months). From the clinical point of view, these data suggest the importance of prolonged medical surveillance while on the stabilization dosage. This is true especially for DD-patients, who take longer to reach their stabilization dosage. Such an attitude can avoid mistaking undermedicated patients for non-responders, particularly when psychiatric illness is present. It follows that, as far as DD-patients are properly managed, and their therapeutic plan adjusted according to their clinical state, the stabilization can be reached as successfully as for

NDD-patients. After the stabilization phase, lasting 8 months on average, methadone tapering can start. Methadone doses administered to DD-patients becomes higher than NDD-patients' as late as in the 8th month. From then on to the end of observation, dosage stays higher for DD-patients, but show the same trend toward decrease as for NDD patients. On the whole, it is advisable to start DD-patients on dosages equal or slightly lower than those administered to NDD-patients, in the first month of treatment. Stabilization dosage must be aimed at for rather a long time (around 5 months); stabilization dosage is expected to be higher (around 140 mg/day) than for NDD-patients. The tapering phase proceeds similarly for both groups. Social adjustment is not likely to be impaired when methadone is being tapered. Data concerning the retention rate corroborate the statement that DD and NDD-patients can equally benefit from MMTP.

5. Conclusions

A third to a half of opiate users may suffer from mental health illnesses, including anxiety, mood disorders, psychotic disorders. Entry into an MM treatment has a significant positive impact in their psychological well-being. These patients may have equivalent outcomes, yet need more attention from clinicians regarding the issue of adequate dosages (lower before the 2nd quarter and higher after the 2nd quarter of treatment). Particular attention is needed when stabilization dosage is to be established, which is expected to take longer in DD than in NDD-patients.

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Contributors

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Conflict of Interest

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