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Evidence of Reliability and Validity of the Opiate Dosage Adequacy Scale (ODAS) in a Sample of Methadone Maintenance Patients

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Summary

Introduction: The testing and adjusting of methadone dosing is a clinical procedure that must be individualized to meet the needs of each patient. So far no evidence has been published of a tool capable of providing a global measurement of dose adequacy. For this reason, we have devised the Opiate Dosage Adequacy Scale (ODAS), which is intended as a means of implementing a theoretical construct called 'dose adequacy'. **Aim:** To provide evidence of the reliability and validity of the ODAS. **Methods:** The study was carried out on a total of 300 patients on MMT, randomly selected from 10 public out-patient drug abuse treatment centres. We used ODAS, Addiction Severity Index (ASI), Outcomes Clinical Impression Form (OCIF) and laboratory tests (serum methadone levels, serum EDDP levels, serum a-1 acid glycoproteins levels [AAG] and urinalysis). **Results:** Internal consistency for the ODAS was acceptable (alpha Cronbach = 0.70). Very high inter-rater reliability was found across items (kappa values between 0.95 and 1). The factor analysis yielded a four factor structure exactly coinciding with the dimensions of the 'dose adequacy' construct proposed a priori ('opiate withdrawal syndrome' 'craving' 'overmedication' and 'drug use'). As far as construct validity is concerned, methadone dose adequacy as measured by the ODAS was correlated with clinical stabilization variables (heroin use, OCIF, ASI), while neither the methadone dose nor SML values correlated significantly with these variables. **Conclusions:** This study provides sufficient evidence for the reliability and validity of the ODAS as a tool for measuring methadone dose adequacy. The results of the construct validity test support the hypothesis put forward by several authors that an individualized clinical assessment of methadone dose adequacy is better able to account for a patient's condition than either the methadone dose or the patient's serum level.

Key Words: Plasma Level, Methadone, Opiates, Assessment, Opiate Dosage Adequacy Scale

1. Introduction

The efficiency and effectiveness of methadone maintenance programmes have been amply documented [24, 64]. The identification of individual prognostic factors

and a knowledge of the programme variables that modulate the therapeutic response are of undoubted practical interest, as these inputs help to improve outcomes [7, 13, 15, 45, 10, 5, 8, 9, 26, 48, 42, 17, 60, 32].

Of the single factors involved, the one that gives

the best results in predicting treatment outcomes is the daily methadone dose taken by the patient [1]. In this connection, it has been demonstrated that subjects receiving the lowest dose have the strongest craving for heroin, and are the most persistent in consuming it, whereas methadone programmes with higher doses have better outcome indicators (e.g., reduction in heroin use, reduction in severity of use-related problems and higher retention rates) [4,1,5,57,58,41,43].

Data drawn from these epidemiological studies cannot, however, be directly extrapolated for application to a specific patient as a basis for methadone dose adjustment. As warned by Maremmani et al. (43), if a study concludes, for example, that doses over 100 mg/day are more effective than doses of 50 mg/day, this should not be interpreted as implying that all patients should receive the highest dose possible. In this sample there would be patients taking 50 or 60 mg/day and responding sufficiently well to treatment, but among the subjects who are receiving the highest doses, the probability of finding good therapeutic outcomes will be higher. The most direct clinical result of these data is that adjustment of the methadone dose must be individualized for each patient. We should therefore not speak of 'high' or 'low' doses as defined in epidemiological studies, but of an 'adequate dose' from an individual clinical perspective [36, 37, 43, 28].

How can it be that patients taking such different methadone doses should display similar clinical efficacy? On the other hand, how is it possible that patients receiving the same methadone dose should show such sharply different responses to it? The reasons must be sought in the clinical pharmacology of methadone. There are pharmacokinetic factors (that mediate the relationship between the dose and plasma levels) and pharmacodynamic factors (that mediate the relationship between plasma levels and effect) which explain the wide variability that has been found in therapeutic responses [65, 22].

Some authors have proposed the routine determination of serum methadone levels (SML) as an instrument able to contribute to the adjustment of the dose in a context of therapeutic drug monitoring, such as the monitoring that is employed with lithium [33, 34, 68]. This type of analysis is based on the existence of a therapeutic SML range between a peak, above which the patient feels overmedication symptoms, and a trough, below which the patient begins to show opiate withdrawal symptoms and signs [50, 36, 51]. With this approach, the purpose of monitoring is to determine the SML of each patient and, if the SML falls outside the therapeutic range, be able to modify his/her methadone dose accordingly. It is true that a great deal of research work has already been done in an attempt to establish this range, but the desired degree of precision has not

been achieved so far [22]. Some studies have proposed a minimum SML threshold needed to eliminate opiate withdrawal symptoms, reduce craving or achieve narcotic blockade, but the figures quoted are very disparate (from 50 to 600 ng/ml), so this information cannot be used to accurately determine the methadone dose that a specific patient needs [2, 34, 39, 67, 68]. Most importantly, there should be no 'high' or 'low' SML, but only an 'adequate SML' for each individual patient, which would be the level at which he/she becomes clinically stable.

It is worth bearing in mind that SML determination only monitors some of the sources of variability in the relationship between methadone dose and its clinical effect (only one aspect of pharmacokinetic variability) [3]. In fact, there are clinical and pharmacodynamic factors, such as the prior tolerance level to other opiates taken previously and genetic polymorphisms associated with the mu-opioid receptor; neither of these can be controlled by SML monitoring, but they certainly influence the clinical response to methadone [63, 30, 35, 40]. In coming years, advances in pharmacogenetics may help to improve the effectiveness of methadone treatment.

Torrens et al. [61] suggest that therapeutic drug monitoring may be useful in assessing compliance with treatment, but not for predicting withdrawal symptoms or heroin use. In this sense, Leavitt et al. [36] believe that SMLs are more appropriate for confirming the inadequacy of a dose than for optimizing one. Okruhlica et al. [49] see SML determination as providing useful orientation when a patient is taking a relatively 'high' dose, his SML is low and he feels craving and/or withdrawal symptoms, which could be pointers to the fast metabolism of methadone. The identification of patients who are fast metabolizers is probably one of the main practical applications of discovering the SML. In this connection, the suggestion of Payte, Zweben and Martín [51] is that an SML peak at 3 or 4 hours after taking the methadone dose should not be more than twice the SML trough (by contrast, a peak/trough ratio over 2 would identify a fast metabolizer).

Assessing and adjusting methadone dosage for each individual patient should remain a basically clinical process [43, 28, 52]. We are in complete agreement with the following statement by Okruhlica et al. [49], "Our findings suggest that neither the daily methadone dose alone, nor methadone concentrations in plasma alone, can be interpreted as a univocal indicator of a patient's stabilization. It is, rather, the criteria derived from assessment of a patient's clinical condition that should set the ultimate guidelines for a doctor's decision as to whether daily doses of methadone in a methadone maintenance programme should be increased or decreased".

To test this hypothesis, a standardized instrument for measuring the clinical stabilization of a patient on a given methadone dose is required. An appropriate dose is usually considered to be one that: a) suppresses the opiate withdrawal symptoms, b) reduces opioid-drug craving, and c) reduces the reward effects of illicit opioids ('blockade') [20, 50, 36, 37, 43]. In research, several different scales have been used to examine items such as withdrawal [25], craving [16], checklists with reported symptoms [21] or analogical-visual scales [59]. Each of these scales, however, measures only one of the items that should be borne in mind when adjusting methadone dosage to optimum levels. For example, doses considered adequate only in terms of withdrawal symptoms will lead to an underestimation of the doses required.

This is why we have designed the Opiate Dosage Adequacy Scale (ODAS) [28], which is intended to provide a means of achieving a theoretical construct called 'adequacy of dosage'. The ODAS attempts to provide clinical measurements of the degree to which a given methadone dose is 'adequate' for an individual patient. The purpose of this paper is to provide evidence of the reliability and validity of the ODAS construct in a sample of patients in a methadone maintenance programme.

2. Methods

2.1 Subjects

The study was performed on a total sample of 300 opiate-dependent patients in treatment in a methadone maintenance programme (MMP) in 10 outpatient centres belonging to the public Provincial Drug Addiction Service of Cadiz. The study design is observational, transversal, and multi-centric. Sampling was random, and was based on quotas, so that each centre participated with a subsample proportional to the total number of patients in the MMP. To be eligible for the study, each patient had to meet the DSM-IV criteria for Opiate Dependence and be an adult under treatment in an MMP for over four weeks. Subjects who, at the time of recruitment or once data collection was already under way, had taken additional unprescribed methadone doses, or had not taken the prescribed dose, were excluded.

2.2 Instruments

2.2.1 Opiate Dosage Adequacy Scale (ODAS)

The Opiate Dosage Adequacy Scale (ODAS) has been designed by F. González-Saiz [28]; it is a brief semi-structured clinical interview whose purpose is

to clinically assess how adequate the methadone dose prescribed in the context of the patient's methadone maintenance programme is to his or her individual needs. This instrument attempts to approximate the construct that we have called "methadone dose adequacy". Operationally, we interpret a methadone dose as being 'adequate' when the patient: a) uses no heroin or uses it only occasionally; b) does not experience continuous opiate withdrawal symptoms (OWS) or, if any, only very mild ones; c) does not experience frequent episodes of craving for heroin, or, if there is any craving, it is very mild; d) in the event of heroin use, the patient does not experience any subjective effects, or any such effects are very mild (narcotic blockade or crossed tolerance); and e) he/she does not experience continuous symptoms of overmedication, or, if any, they are very mild. The ODAS is designed to assess the degree of adequacy of the dose taken by the patient during the previous seven days or so. As a minimum, therefore, the patient has to continue on that same dose during this period to ensure that he has reached the steady state for that dose.

The ODAS clinical interview comprises 10 items that evaluate the six specific attributes or components of the 'dose adequacy' construct: Continuous use of heroin (Item 1); Narcotic blockade or crossed tolerance (Item 2); Objective OWS (Items 3a and 3b); Subjective OWS (Items 4a and 4b); Craving for heroin (Items 5a and 5b); and Overmedication (Items 6a and 6b). For further information on the ODAS, see the general instructions in the Appendix. This instrument includes the five Additional Items that record complementary information that the clinic may take into consideration before making its decision on whether to modify the methadone dose. These items do not form part of the ODAS proper, so they have not been included in the quantitative scoring.

The questions that measure the frequency of symptoms are coded by Likert-type scores from 1 to 5, and the questions that measure severity of symptoms follow an analogical-visual scale with the same range of scores. ODAS scores may be interpreted both quantitatively (dimensional model) and qualitatively (categorical model). First, they provide a total score from the weighted sum of individual item scores. The higher the total score, the more 'adequate' the dose is. Second, at a certain cut-off point, each patient's dose can be categorized as 'adequate' or 'inadequate'. ODAS score derivation is explained at the end in the Appendix.

According to clinical pharmacology nomenclature, the ODAS measures the pharmacological effect, that is, the optimal clinical effect most directly dependent on a certain methadone dose. In our opinion, it is important to differentiate between this pharmacological effect and a patient's stabilization after he/she has been on the MMP for a time (outcomes). An adequate methadone

dose is a necessary condition, but it is insufficient to ensure a good response to treatment, since it depends on a variety of predictive factors (i.e. psychosocial intervention, diagnosis and treatment of the psychiatric comorbidity).

2.2.2 Addiction Severity Index (ASI)

It is a semi-structured clinical interview for the purpose of evaluating drug use-related problems [46]. It consists of six individual scales which assign a score to the severity of each of these problems (medical, legal, substance abuse, employment, family and psychological function). Each scale has two types of total scores called Severity Ratings and Composite Scores. It should be noted that some studies have used the items on each scale that measure the frequency of problems over the last month as outcome variables, since it has been demonstrated that these items are especially sensitive to change [1]. One recent study proposes the construction of an aggregate outcome index derived from the weighted sum of these items on the ASI [29]. In our investigation we have used a simplified form of this Aggregate Outcome Index (SF-AOI) as an overall indicator of addiction severity. The validated Spanish version of the ASI [27] was used for this.

2.2.3 Outcome Clinical Impression Form (OCIF).

The overall clinical condition of each patient and the degree of response to the MMP were assessed using the Outcome Clinical Impression Form (OCIF). First, each patient's case-manager (physician, psychologist or social worker) was asked to qualitatively formulate his impression of the clinical progress of his/her patient and the degree of overall response to the MMP, keeping in mind the severity at time of admission and the individual therapeutic goals posed. This description was not to exceed 100 words. Second, an independent researcher not involved in the MMP coded these descriptions, and classified the level of treatment response as Low, Moderate or Good. Finally, an addiction psychiatrist not working in the treatment programmes supervised this assignment process, reaching a consensus with the researcher on initially conflicting coding. The whole coding process was blind to other clinical measurements.

2.2.4 Data Logbook (DLB).

Sociodemographic variables, drug abuse history, health problems, background of previous treatments and variables related to the current MMP were recorded in a Data Logbook (DLB).

2.2.5 Laboratory tests:

Serum Methadone Levels (SML) (trough level) analysis was performed by homogeneous enzyme immunoassay (EIA) using CEDIA[®] technology on complete blood samples in a Hitachi 911 autoanalyser from Mycrogenics (Boehringer Mannheim Corp.). Methadone metabolite EDDP levels and alpha-1-acid glycoprotein (AAG) concentration in plasma were measured, too.

Urine was tested for the metabolites of abuse substances (methadone, heroin, cocaine, benzodiazepines, amphetamines and cannabis), and general biochemistry.

2.3 Procedure

The study was jointly carried out by the Clinical Pharmacology Department of the Hospital de Puerto Real (University of Cadiz) and by the Information Systems and Research Area of the Andalusian Foundation for Drug and Alcohol Dependence (FADA), in cooperation with the medical staff of the Provincial Drug Addiction Service of Cadiz.

After the sample had been randomized by the researchers and a subsample had been assigned to each of the 10 participating centres, the physician in each service made appointments with the candidate patients for an initial interview and informed them individually of the purposes of the study, performed the testing for the selection criteria and asked each candidate patient to sign the informed consent form. Each physician filled out the Data Logbook with the information contained in the patient's clinical history and the information acquired in the interview, except for the Outcome Clinical Impression Form, which was filled in by the case-manager.

Patients were called for a second interview by a team of researchers not involved in the MMP. This team was made up of a physician specialized in clinical pharmacology and by a nurse. The nurse took the blood samples just before administering the daily dose of methadone (SML trough), then the patient provided a urine sample for the drug metabolite test. The clinical pharmacologist interviewed the patient using the ODAS and ASI (SF-AOI) scales and supervised the entire process. The patients were given 12€ as payment for their participation in the study.

2.4 Statistical Analyses

Chronbach's alpha was calculated for an analysis of ODAS internal consistency. This varied between 0 and 1 (14), which was interpreted according to the

Table 1. Patients with “adequate dose” according to the ODAS and their relationship with the mean dose ranges and mean methadone plasma levels

	n	(%)	Methadone dose (mg/day) ¹		Methadone plasma level (ng/ml)	
			Mean	(s.D.)	Mean	(s.D.)
“Adequate”	179	(59.6)	66.5	(55.4)	215.7	(159.9)
“Inadequate”	121	(40.3)	83.3	(58.8)	251.5	(188.1)

¹. Significant differences for $\alpha=0.05$

criteria of Nunnally [47], who considers values under 0.60 insufficient.

To evaluate inter-rater reliability, the following procedure was employed: The clinical pharmacologist interviewed the patient directly using the ODAS, and the nurse simultaneously assigned a score to the subject’s responses to the questions asked by the main interviewer on a blind parallel questionnaire. This was done for a total of 140 subjects. Analysis of this type of reliability was carried out item by item, estimating the value of the weighted kappa coefficient, which represents the concordance between items corrected for chance agreement (12), for each pair. For k the guidelines for clinical significance are as follows: below 0.40 is poor, from 0.41 to 0.59 is fair, from 0.60 to 0.74 is good, and above 0.75 is excellent (Cicchetti’s criteria)[11]. The Intraclass Coefficient Correlation (ICC) by Shrout and Fleiss [54] (Form [1.1]) was used to calculate the agreement between total ODAS scores. The ICC is derived from summarized information taken from the results of the Analysis of Variance (ANOVA) applied to these repeated measurements. Verification of their reliability was based on the hypothesis that the differences found between the two interviewers for each subject (‘intra-subject’ variability or quadratic mean) must be fewer than the differences between the scores of the subjects observed by the same interviewer (‘between-subject’ variability or quadratic mean). Qualitative interpretations of the ICC were based on the recommended ranges of clinical significance specified by Cicchetti [11].

To evaluate the dimensionality of the ODAS, a factorial analysis was performed using an exploratory analysis (Principal Components Analysis). To determine the number of factors to be extracted we followed the criteria of Kaiser [31], and for the selection of saturating items in each factor, the criteria of Stevens [56]. Varimax rotation was used for solution transformation.

The relationship between the adequacy of the methadone dose (ODAS scores) and a set of variables that define clinical patient stabilization was evaluated. This analysis appears to contribute evidence on the concurrent validity of the ODAS. We also wished to simultaneously test the hypothesis that clinical evaluation of methadone dose adjustment (as measured by the ODAS) predicts the clinical response of the pa-

tient better than the methadone dose alone and than the SML alone, as proposed by Okruhlica et al. [49]. The variables considered as indicators of a patient’s stabilization were:

- 1) Percentage of urine tests positive for illicit opiates in the last week;
- 2) Days heroin was used in the last month;
- 3) Clinical impression of patient progress in the MMP (Outcome Clinical Impression Form: OCIF);
- 4) Severity of use-related problems (simplified ASI Aggregate Outcome Index form ASI - SFAOI).

Lastly, we analyzed the relationship between the ODAS scores and the other nomothetic variables of this construct, such as:

- 1) Patient’s subjective evaluation of the adequacy of his/her dose (as measured by the corresponding Additional Item A in the ODAS);
- 2) Desire to modify the current methadone dose (as measured by the corresponding Additional Item B in the ODAS);
- 3) Secondary effects of the methadone treatment (Additional Item C).

3. Results

3.1 Sample Characteristics

The subjects in the sample studied have an average age of 38.5 years (s.d. 6.7); most of them were men (83.6%). Before beginning methadone treatment, 68.2% were out of work and 76.8% had committed some kind of crime. The mean body mass index was 23.4 (s.d. 4.5). 79.5% of the sample had previously been in some other type of treatment for their addiction. From the beginning of the methadone programme, the subjects attended an average 82% of the appointments fixed for them (“adherence to MMP” is defined as the ratio between the number of appointments the patient kept and the total number of appointments made). The patients in the sample had been in treatment on methadone for an average of 47.3 months (range: 1-124 months). 30.3% of the patients went daily for a directly observed methadone dose and the remaining 69.7% had authorization for weekly take-home doses (either the patient himself/herself or an authorized family member went

to the dispensing point to collect the corresponding methadone tablets.)

The average methadone dose in the sample was 75.5 mg/day (s.d. 57.8), ranging from 2.5 mg/day to 400 mg/day. Table 1 shows that 59.6% of the subjects in the sample received an 'adequate' methadone dose, and that it is properly adjusted according to the ODAS, while the dose of the remaining 40.3% was considered to be 'inadequate'. The average daily methadone doses are shown in this table, together with the mean SML for each of the two classes of adequacy.

The Additional Items in the ODAS provide complementary clinical information that can be helpful in

	N	(%)
Constipation	126	(41.9)
Increased sweating	140	(46.5)
Insomnia or difficulty in sleeping	183	(60.8)
Altered sexual functioning	94	(31.2)
Altered menstrual functioning	24	(48%)*
Tiredness	165	(54.8)
Nausea	89	(29.6)

* Percentage of total number of women

reaching a decision on methadone dose changes. Additional Item A evaluates the subjective perception by the patient of how adequate his/her dose is (the higher the score, the more adequate it is perceived to be). The average score in the sample on this item is 4.2 out of a maximum of 5 (s.d. 1.2). As to user satisfaction with their current methadone dose (Additional Item B), 50.2% of the patients expressed their desire to continue on their present dose, 10.3% wanted to increase it and 39.55% wanted to decrease it. As shown in Table 2, the secondary effect most frequently observed in this sample was insomnia, followed by a feeling of tiredness and increased sweating (Additional Item C).

The Pearson correlation coefficient between methadone dose and plasma level is 0.57 ($p < 0.05$). Between methadone dose and total ODAS score (degree of adequacy), the correlation observed is -0.13 ($p < 0.05$). Lastly, between plasma level and total ODAS score, a correlation coefficient of -0.025 ($p < 0.05$) is observed.

3.2 Reliability

3.2.1 Internal consistency

The Chronbach Alpha coefficient observed is 0.70, which is sufficient according to the Nunnally criteria [47]. This means there is acceptable covariance among the items in the ODAS, which appears to support its

	Weighted Kappa
1. Continued heroin use	1
2. "Narcotic blockade" (Crossed tolerance)	1
3a. Frequency of objective OWS	0.98
3b. Intensity of objective OWS	0.95
4a. Frequency of subjective OWS	0.96
4b. Intensity of subjective OWS	0.96
5a. Frequency of craving heroin	0.98
5b. Intensity of craving heroin	0.98
6a. Frequency of overmedication	0.94
6b. Intensity of overmedication	1

internal consistency.

3.2.2 Inter-rater reliability

Table 3 shows the weighted kappa coefficients for each of the items in the ODAS. It may be observed that these values are very high, all of them within the category of "excellent" according to the criteria of Cicchetti [11], which supports the inter-rater reliability of this scale. The intraclass correlation coefficient, too, is very high ($ICC = 0.98$), which indicates close concordance among total scores on the scale to be administered by different evaluators.

3.3 Validity

3.3.1 Factorial analysis

Analysis of the main components shows a four-factor structure which coincides precisely with the dimensions of the "dose adequacy" construct proposed a priori (see Table 4). The first factor, which we call "OWS", clusters the four items that evaluate the frequency and intensity of the objective and subjective opiate abstinence symptoms and explains 29.7% of the variance in the correlation matrix ($\lambda = 2.9$). The second factor (which we call "craving") saturates the items that evaluate the frequency and intensity of craving for heroin, and accounts for 21% of the variance. The third factor clusters the items that evaluate "overmedication" and the fourth and last factor, which we call "consumption", saturates the items on consumption frequency in the previous week and the degree of narcotic blockade.

Once the dimensional structure of the scale had been identified, we carried out a reliability analysis for each of these dimensions. Thus, the "OWS" factor turned

Table 4. Factorial analysis of items on the ODAS

	Factor 1	Factor 2	Factor 3	Factor 4
1. Continued heroin use	0.032	0.313	-0.021	0.802
2. "Narcotic blockade" (Crossed tolerance)	0.008	0.004	-0.016	0.900
3a. Frequency of objective OWS	0.793	0.107	-0.021	-0.057
3b. Intensity of objective OWS	0.819	0.090	-0.030	-0.013
4a. Frequency of subjective OWS	0.849	0.033	-0.059	0.026
4b. Intensity of subjective OWS	0.836	-0.045	-0.059	0.107
5a. Frequency of craving heroin	0.064	0.944	-0.023	0.172
5b. Intensity of craving heroin	0.083	0.950	-0.020	0.101
6a. Frequency of overmedication	-0.062	-0.022	0.971	-0.022
6b. Intensity of overmedication	-0.065	-0.020	0.970	-0.016
Eigen value	2.97	2.10	1.82	1.17
Percentage of variance	29.73	21.04	18.16	11.65

out to have a Chronbach's Alpha Coefficient of 0.84, the "craving" factor 0.92, "overmedication" 0.92 and, lastly, "consumption" had a coefficient of 0.67. As may be observed, these values support high internal consistency for each of the scale's dimensions.

3.3.2 Relationship of the construct measured with the ODAS and clinical stabilization variables

The mean ODAS score is higher for patients who are abstaining from heroin, as measured by urine analysis, than for those still consuming it; this difference is statistically significant. On the other hand, no significant differences were observed between average

methadone doses in the two groups of patients. Nor is there any statistically significant difference in plasma levels (see Table 5).

What is more, there is a statistically significant negative correlation ($r = -0.29$) between ODAS scores and the number of days when heroin was consumed during the previous month (that is, the more adequate the dose, the lower the consumption frequency). Conversely, no significant association can be found between the mean methadone dose or plasma levels, and the number of days when heroin was consumed during the last month (Table 5).

Among patients showing better clinical progress, as measured by their case-managers using the Outcome

Table 5. Analysis of the relationship of the construct measured with the ODAS and clinical stabilisation variables

	Heroin use			Outcome Clinical Impression Form (OCIF)			Aggregate Outcome Index (ASI)
	Opiate metabolites in urine (ANOVA)		N° of days used in the last month (C. Pearson)	Low N=34	Moderate N=42	Good N=129	
	Positive N = 42	Negative N = 258					
Methadone dose adequacy (Total ODAS score)	26.1	27.4 **	R = -0.29 **	25.4	26.9	27.4**	R = -0.30**
Methadone dose (mg/ml)	70.5	73.6 (ns)	R = -0.006 (ns)	82 (ns)	67.1	71.3	R = 0.07 (ns)
Methadone plasma level (ng/ml)	219.4	249.1 (ns)	R = -0.04 (ns)	242.7 (ns)	213	240.1	R = 0.07 (ns)

* $p < 0.05$; ** $p = 0.01$; ns = not significant

Clinical Impression Form scale, the mean scores on the ODAS are higher, too, and these differences are statistically significant. However, there are no significant differences between these three groups of patients based on methadone dose or plasma levels.

Lastly, a statistically significant negative correlation can be observed ($r = -0.30$) between ODAS scores and scores on the ASI Aggregate Outcome Index. In other words, the better adjusted the methadone doses measured by the ODAS, the fewer heroin use-related problems there are. On the other hand, no significant correlation is found between average methadone dose or plasma levels and the Aggregate Outcome Index.

3.3.3 Relationship between the constructs measured using the ODAS and other nomothetic variables (Additional ODAS Items)

3.3.3.1. Subjective patient evaluation of the adequacy of his/her methadone dose (Additional Item A)

A statistically significant correlation ($r = 0.47$; $p < 0.01$) can be observed between the total ODAS score and the subjective evaluation which the patient himself makes of how well his methadone dose is adjusted. In other words, there appears to be an acceptable concordance between the adequacy as evaluated by the clinician on the basis of the information supplied by the patient, and the subjective evaluation of the patient himself.

3.3.3.2. Patient's desire to modify his/her methadone dose (Additional Item B)

The multiple Bonferroni test comparisons indicate that there are statistically significant differences ($p < 0.05$) between those who wish to increase their methadone dose (worse average adjustment [24.4]) and those who wish to maintain (27.5) or decrease it (27.7). There are no significant differences between these last two categories..

3.3.3.3. Secondary effects of methadone taken during the last week (Additional Item C)

Lastly, a moderate statistically significant negative correlation ($r = -0.37$; $p < 0.01$) can be observed between the total score on the ODAS and the number of secondary effects of the methadone treatment. That is, there appears to be an association between good adjustment of the methadone dose and fewer secondary effects.

4. Discussion

The data contributed by this research work provide sufficient evidence of the reliability and validity of the

ODAS when it is used as an instrument of measurement and assessment of the adequacy of the methadone dose taken by a patient in the context of an opiate dependence treatment programme.

The internal consistency of the scale is sufficient according to the criteria of Nunnally [47] and according to the recommendations of Dennis et al. for the requirements for an addictive disorder evaluation instrument [19]. This seems to indicate that all the items on the ODAS are strongly related to each other, and in the same direction. Moreover, the degree of agreement observed between clinicians is very high (inter-rater reliability), which helps minimize the different sources of diagnostic variability described by Spitzer et al. in the use of a measurement instrument in clinical practice or research [55].

Our theoretical proposal of the construct 'dose adequacy' is, on one hand, based on a review of the literature and the opinions of relevant authors [22, 50, 36, 37, 43, 49] and, on the other, on our own clinical experience subjected to reflection and review. Factorial analysis of the ODAS identifies four factors ("OWS", "craving", "overmedication" and "heroin consumption"). In our opinion, it is worth mentioning the coincidence of this structure with the dimensions proposed a priori for this construct, which we interpret as empirical support for it [28]. All of the items on the scale, bar none, saturate the four factors identified by the model as a solution for the matrix of correlations. In other words, all of these items appear to be "necessary" in explaining and defining the 'adequacy' construct. This, along with the internal consistency, go to indicate that the ODAS appears to measure a homogeneous (as a whole) and, at the same time, multidimensional construct. Each of these dimensions, in turn, appears to display a very high degree of internal consistency.

Another outstanding fact in this factorial analysis is the distribution of the percentages of variance accounted for by each of the factors. Percentages are observed to be well distributed, which implies that all of the factors have an excellent 'weight' within the construct. The OWS items explain a major percentage of the instrument's variance, followed by the items that saturate the 'craving' and 'overmedication' factors. To a certain extent, this weighting and this order may also be observed in clinical practice during the process of induction into methadone treatment. The goal of the early doses is to decrease or eliminate the symptoms of the objective OWS, and with each successive increase after a steady state is reached, a reduction in the subjective OWS symptoms and craving can be observed [65, 36, 51, 43]. In our opinion, an 'adequate' dose appears to fall within a hypothetical 'individual therapeutic range', that is, a dose that is high enough to achieve an 'anti-craving' effect, but not high enough to induce

symptoms of overmedication. In our experience, it is clear that this therapeutic range (regardless of the dose that defines it in each patient) varies widely. For example, for some patients the 'anti-craving' dose is very near to the dose at which overmedication symptoms begin to appear, whereas other patients tolerate the drug well when it is given at effective doses. Situating the patient within this therapeutic range is a crucial concern, since a reduction in the continued consumption of heroin usually takes place when he/she reaches the 'anti-craving' dose, which is usually (but not always) associated with achieving a narcotic blockade.

This is precisely one of the hypotheses that we are trying to test: that is, an 'adequate' dose, as measured by the ODAS, should be related to clinical stabilization of the patient. In this sense, the data in this research work support the existence of a clear and significant relationship between a more adequate methadone dose and a reduction in heroin consumption, a favourable evaluation by the case-managers and fewer heroin use-related problems. These results appear to contribute evidence on the validity of the ODAS construct. In addition to this conclusion, the data reported in this paper provide empirical support for the hypothesis proposed by Okrulika et al. [49], that is, neither the methadone dose nor the SML alone appear to satisfactorily account for the patient's clinical stabilization. As shown by our clinical experience and common sense, it is the clinical assessment of the patient (individual response to a certain methadone dose) which must be considered in deciding whether it should be changed; in addition, this assessment seems to be associated with the patient's clinical improvement.

Moreover, the relationship between the 'adequacy' construct and other variables of interest has been explored, too. The patients in the sample are observed to have a subjective perception of the methadone dose they are taking as 'adequate', that is, they perceive that their dose is helping them to reduce their continuing consumption of heroin, because they do not experience withdrawal symptoms or craving for heroin, but do not feel overdosed, either. It is precisely the patients that record the highest scores on the ODAS who evaluate the adequacy of the dose they are taking most positively. Similar results have been observed by Pérez de los Cobos et al. [53], in employing an analogical-visual scale to evaluate the overall adjustment of the methadone dose perceived by patients. Lastly, it is observed that the more adequate the methadone dose is, the fewer the secondary effects it has. Conversely, it is interesting to note that higher doses are associated with more secondary effects ($r = 0.13$; $p < 0.05$) and higher plasma levels, too, correlated with more secondary effects ($r = 0.12$; $p < 0.05$), even if the correlation coefficients are lower.

As shown in Table 1, there is considerable over-

lapping of the methadone dose between patients with 'adequate' and 'inadequate' doses (see s.d. values). For example, there appear to be patients taking a 70 mg/day dose that is considered 'adequate' (effective) according to the ODAS, whereas in other patients, this same dose may be assessed as 'inadequate' (ineffective) and it would therefore have to be increased. Trafton et al (62) find this same overlapping and arrive at the same conclusion by employing as their criterion for an "effective dose", a dose that enables a patient to stay off heroin for longer than one month. This, along with the above discussion on secondary effects, again provides support for the hypothesis that there is no such thing as 'high' and 'low' methadone doses in absolute terms, but only 'adequate' ones. In other words, what is really important from the clinical viewpoint is not that the patient should take the highest dose possible, but, whether the dose is 'high' or 'low', that it should be the most 'adequate' one for each individual patient.

In the sample studied, almost 60% of the subjects appear to have received an 'adequate' dose. In our health-care network there is no policy on methadone dose limitation and, in general, the philosophy of the staff is oriented towards maintenance in line with the paradigm of harm reduction. If a patient does not receive a higher methadone dose, it is generally because he or she does not want to increase it. In our environment, it is usually patients who request a methadone dose that is relatively low', in the sense of being sufficient to avoid objective OWS symptoms, but not high enough to implement a narcotic blockade. This enables them to start the day without any urgent need to take heroin, but, independently of whether it is consumed together with alcohol or benzodiazepines (generally alprazolam), they experience an effect of euphoria/sedation. In this context, we distinguish between an 'adequate dose' and a 'dose accepted by staff', that is, a dose which in principle is pharmacologically 'inadequate' but which, owing to patients' retention in the methadone programme, actually allows them to meet intermediate health goals (treatment for HIV infection and HCV, tuberculosis, psychiatric treatment), social integration, employment and quality of life.

In the sample studied, the correlation coefficient observed between methadone dose and plasma levels is considerably lower than those found by other authors [67, 33, 34]. In our opinion, this is due to the 'naturalistic' design of our study since, unlike other authors, we did not exclude any patients because they were taking antiretroviral agents, tuberculostatics or other types of drug, or because of their medical or psychiatric condition. That leads us to believe that a correlation coefficient of 0.57 must be a figure close to to the clinical reality in which we work. On the other hand, the correlation between methadone dose and its

“pharmacological effect” (as measured by the ODAS) can be acknowledged to be insufficient. Even more evident is the absence of linkage between the SML and the “pharmacological effect”. The most important requirement for a drug to be subject to monitoring is that there should be linkage between its concentration in plasma and its pharmacological effect, because otherwise it would be pointless to try to measure it [3]. Thus, the data reported in this study do not justify systematic monitoring to determine the SML (that is, as a dose adjustment tool for placing the dose to be prescribed within the therapeutic range). In any case, our data fail to provide grounds for considering the clinical assessment of patients - in the attempt to achieve adequacy as measured by the ODAS - the most useful instrument for making a decision on whether to modify the methadone dose. Even so, we believe that determining the SML could offer a useful way to a) evaluate compliance with the dose, as pointed out by Torrens et al. [61], and b) facilitate the diagnosis of a fast metabolizer (that is, a case in which the peak/trough ratio is over 2). In this context, Baño et al [38]. propose a promising algorithm for the integration of clinical information with that contributed by the SML in making methadone dose adjustment decisions.

One of the basic hypotheses of our research work was that among the patients with the highest methadone doses, we would find the highest ODAS scores, or at least a higher percentage of subjects with ‘adequate’ doses’. Unexpectedly, we did not observe this in our sample (see Table 1 and the correlation coefficient between methadone dose and ODAS scores). In our opinion, this result may be due to the sample studied being made up of stabilized patients who had been on treatment with methadone for quite some time. For example, many of the patients with doses under 60 mg/day had been gradually reducing their dose. This same phenomenon has been observed by Willenbring et al. [66], who found that treatment centres with a low level of patient turnover and a high percentage of stabilized patients in maintenance may achieve good results despite the prescription of relatively low doses. We should not forget that in these cases there has been a gradual reduction in tolerance and neuroadaptation, so that, for example, a dose as low as 30 or 40 mg/day might prove to be ‘adequate’. Another factor that could explain relatively low ODAS scores in patients with high methadone doses is the high prevalence of cocaine abuse. In our environment, heroin is preferentially inhaled-smoked (95%) in combination with cocaine (a mixture called “rebujao”). This type of patient would try to experience the effects of cocaine more than those of heroin, and in the therapeutic approach this is usually associated with an increase in the methadone dose. These ‘unexpected’ effects often turn out to be quite

common in treating patients with multiple substance abuse [23].

One of the limitations of our study is precisely that it was performed on a sample of very stable patients who had been in an MMP for a long time. It would be of interest for future studies on this scale to perform an evaluation of patients during their first few weeks in the programme (methadone induction), up to the moment of their stabilization. Furthermore, more evidence on the concurrent validity of the EADO is required. Specifically, it would be worth studying the relationship between the items on this scale with parallel measurements and then going on to analyse it with a multi-method-multi-trait matrix, for instance, the objective and subjective OWS items with specific OWS scales or the craving items with another scale on craving.

Another limitation of our work is its transversal design. Future longitudinal studies should attempt to incorporate ‘adequacy’ sequentially and relate it to measurements of treatment outcomes. Although this study was performed on a sample of patients already on methadone treatment, the ODAS is also designed to evaluate the adequacy of buprenorphine doses. Therefore, future studies should aim to provide evidence on patients taking buprenorphine.

This research work contributes more evidence on ODAS dimensional scoring than on its categorical scoring. Our recommendation is that dimensional scoring

Appendix 1. ODAS Scoring Code

Dimensional Scoring

Item 1: Scores from 1 to 5

Item 2: Scores from 1 to 5

Item 3 (objective OWS):

Item 3a: Scores from 1 to 5

Item 3b:

If the score on 3b is 1 or 2 (that is, a very intense objective OWS), one point is subtracted from Item 3a (example: if 3a scores 4 and 3b scores 2, then “Item 3” scores 3).

If the score on 3b is 3, 4 or 5: the score in Item 3a is not changed (and this will therefore be the score for “Item 3”).

Items 4, 5 and 6: score using the same procedure as for Item 3.

Therefore, the total score on the ODAS is the sum of the scores of each one of the 6 items in a range of 6 to 30 points.

Categorical scoring:

A patient is considered to have the “adequate dose” when the 6 items in the ODAS (scored following the procedure defined in “Dimensional scoring”) SCORES 4 OR 5. Those who do not meet this condition are not classified as patients with an “adequate dose”.

should always be employed, both for both clinical and research applications. The transformation of a dimensional measure into a categorical one always means a loss of information, in addition to the difficulty of deciding on a cut-off point (44). The categorization of a measurement may be worthwhile when a diagnostic or therapeutic decision depends on it. We have chosen a clinical criterion based on the literature to establish the cut-off point by differentiating between 'adequate' and 'inadequate', but we understand that other colleagues may not concur with this criterion.

This work contributes sufficient evidence on the psychometric quality of the ODAS, and we believe that it constitutes a good working tool, whether in clinical practice or in research; in addition, it opens up new lines of study.

5. Conclusions

This study provides sufficient evidence for the reliability and validity of the ODAS as a tool for measuring methadone dose adequacy. The results of the construct validity test support the hypothesis put forward by several authors that an individualized clinical assessment of methadone dose adequacy is better able to account for a patient's condition than either the methadone dose or the patient's serum level.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.

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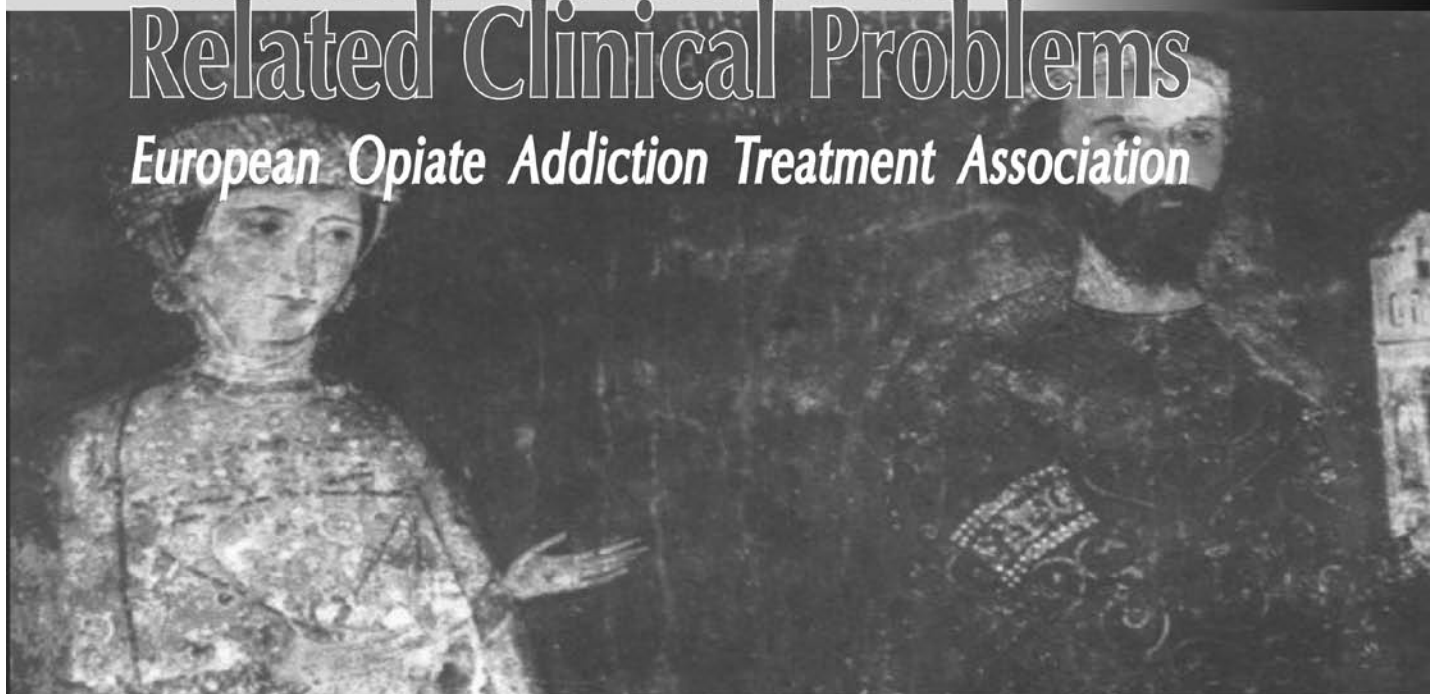
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