Methadone dosage and its relationship to quality of life, satisfaction, psychopathology, cognitive performance and additional consumption of non-prescribed drugs

Dosis de metadona y su relación con calidad de vida, satisfacción, psicopatología, rendimiento cognitivo y consumo adicional de sustancias no prescritas

Eduardo J. Pedrero-Pérez*, Grupo MethaQoL**

* Instituto de Adicciones. Madrid Salud; ** Instituto de Adicciones. Madrid Salud y Junta de Extremadura (listado completo al final).

Abstract

The effectiveness of methadone maintenance treatment is beyond any doubt, but there remains some incertitude about the appropriate and effective dosage and the objectives that should be achieved by this therapy. Some authors maintain that only doses higher than 50-60 mg/day ought to be considered effective, since only these block all the opioid receptors. But others propose the use of doses adjusted to the needs of the patient, based on their recovery process. Quality of life, satisfaction with treatment, psychopathological symptoms, cognitive performance and additional intake of illegal and unprescribed drugs were evaluated in a representative sample of all patients treated with opioid agonists in the Addiction Institute of Madrid (N = 1898, n = 450) and the Junta de Extremadura (N = 100, n = 65). The results revealed a negative relationship between dose and quality of life, psychopathological symptoms and cognitive performance. Satisfaction with treatment, based on doses negotiated together by doctor and patient, was very high, regardless of the dose. To establish hypothetical causal dependencies among the studied variables structural equation modelling was performed. The results reject the need for high dosage if not required by the patient, and highlight the benefits of other psychosocial interventions that lead to recovery, despite the chronification that could imply the use of high doses. Whereas high dosage programmes provide better indicators of social control, the patient's quality of life must be one of the main indicators of a successful treatment, as in any other health problem.

Keywords: Methadone Maintenance; Dosage; Quality of Life; Addiction; Treatment.

Resumen

La efectividad de los tratamientos con metadona está fuera de toda duda, si bien persisten dudas sobre las dosis efectivas y los objetivos que debe perseguir un programa de mantenimiento. Algunos autores propugnan que sólo superiores a 50-60 mg/día deben ser consideradas efectivas, al bloquear los receptores opioides. Otros proponen dosis ajustadas a las necesidades del paciente, atendiendo prioritariamente a su recuperación. Se estudió una muestra representativa de todos los pacientes en tratamiento con agonistas del Instituto de Adicciones de Madrid (N=1898, n=450) y de la Junta de Extremadura (N=100, n=65). Se evaluaron calidad de vida, satisfacción con el tratamiento, sintomatología psicopatológica, rendimiento cognitivo y consumos adicionales. Los resultados muestran una relación negativa entre dosis y calidad de vida, sintomatología psicopatológica y rendimiento cognitivo. La satisfacción con el tratamiento, basado en dosis negociadas entre médico y paciente, fue muy elevada, con independencia de la dosis. Se formuló una ecuación estructural que relacionara todas las variables. Los resultados descartan la necesidad de utilizar dosis altas si el paciente no las precisa, y contar con otras intervenciones psicosociales que favorezcan la recuperación frente a la cronificación que supone el uso de dosis altas. Mientras los programas de altas dosis atienden prioritariamente a indicadores de control social, la calidad de vida del paciente debe ser uno de los principales indicadores de éxito del tratamiento, como en cualquier otro problema de salud.

Palabras clave: Mantenimiento con metadona; Dosis; Calidad de vida; Adicción; Tratamiento.

Received: September 2015; Accepted: November 2015

Send correspondence to:
Eduardo J. Pedrero Pérez. C/ Alcalá 527, 28027 Madrid.
E-mail: ejpedrero@yahoo.es

The efficacy, effectiveness and efficiency of methadone maintenance treatment for heroin addiction is currently beyond any doubt (Mattick, Breen, Kimber & Davoli, 2009). Uncertainty persists, however, as to the most effective doses and the objectives of a maintenance programme.

The currently predominant approach advocates doses higher than 50-60 mg/day (90-100 mg on average), and has three primary objectives: (a) suppression of symptoms on withdrawal of exogenous opioids; (b) cessation of craving; (c) pharmacological blocking of the reinforcing capacity of heroin in the saturation of opioid receptors (Maremmani, Pacini, Lubrano & Lovrecic, 2003). The chief indicators of successful treatment are reduction of heroin and cocaine consumption, reduction of the seriousness of problems linked to consumption, and greater retention rates. This approach focuses primarily on the pharmacological effects of opioids and their capacity for blocking receptors (Pacini, Maremmani, Rovai, Rugani & Maremmani, 2010). Various studies (for example Adelson *et al.*, 2013; Faggiano, Vigna-Taglianti, Versino & Lemma, 2003; Farré, Mas, Torrens, Moreno & Camí, 2002) have found that higher doses correspond to longer treatment times and lower consumption of heroin and other drugs. Patients with comorbid psychopathology need higher doses, 150mg/day, compared to those presenting only opioid addiction, who require 100mg/day on average (Eiden, Leglis, Clarivet, Blayac & Peyrière, 2012). Other authors even advocate very high doses (from 100 to 780 mg/day) as "necessary" to prevent opioid consumption and control concurrent psychopathology (Maxwell & Shinderman, 1999).

The above approach has been criticised for ignoring other issues such as the perspectives of the patients themselves or the need to deal primarily with other problems and risks. It must be remembered that, along with other opioids (Katz, 2005; Benyamin *et al.*, 2008), methadone is not a drug devoid of any undesirable side effects (Bell & Zador, 2000; Bileviciute-Ljungar, Häglund, Carlsson & von Heijne, 2014; Chugh *et al.*, 2008; Grönbladh & Öhlund, 2011; Webster, 2013), which are all the more intense and likely to occur the higher the dose (Leavitt, 2003; Walker, Klein & Kasza, 2003). Grave complications are not uncommon at high doses (Krantz, Kutinsky, Robertson & Mehler, 2003), and even at more moderate doses (Krantz, Martin, Stimmel, Mehta & Haigney, 2009; Roy *et al.*, 2012). Among these side effects, deficiencies in neuropsychological performance are some of the most frequently encountered (Bracken *et al.*, 2012; Gruber *et al.*, 2006; Loeber, Kniest, Diehl, Mann & Croissant, 2008; Mintzer, Copersino & Stitzer, 2005; Mintzer & Stitzer, 2002; Rass *et al.*, 2014) and their frequency increases with the dose (Rass *et al.*, 2014). Patients under methadone treatment presented significant cognitive deficits, while those in prolonged opioid abstinence and without treatment performed significantly better (Verdejo, Toribio, Orozco, Puente & Pérez-García, 2005), even as controls (Darke, McDonald, Kaye & Torok, 2012).

Another approach has been the so-called low threshold programmes, the main objective of which is not necessarily to eliminate the use of illicit drugs entirely but rather to establish and maintain contact with opioid users with the aim of helping to stabilize and reduce some of the associated risks and develop the confidence necessary to help them aspire to more ambitious objectives in later treatment phases (Hartgers, van den Hoek, Krijnen & Coutinho, 1992). There is plenty of empirical evidence pointing to a substantial improvement in the quality of life of these patients and a reduction of the risk of serious complications, even though consumption is not completely stopped (e.g., Brugal *et al.*, 2005; Millson *et al.*, 2007; Torrens, Castillo & Perez-Sola, 1996; Villeneuve *et al.*, 2006). Some studies show that retention in this kind of programme is not lower than in others which use higher doses (Perreault *et al.*, 2007) and which can favour the incorporation of other modes of treatment as required (Schwartz *et al.*, 2006).

A third line of treatment is characterised by focusing on the improvement in the quality of life without special attention to the doses required to achieve this. When considering the patient's quality of life it is also necessary to bear in mind the need for psychosocial interventions to avoid the negative consequences of the treatments, for example stigmatisation, discrimination, methadone dependence and the paralysing effects of the drug on the emotions (De Maeyer, Vanderplasschen, Camfield *et al.*, 2011; Harris & McElrath, 2012). The success of the treatments depends of other factors, such as work, family relationships, availability of intimate relationships, scheduling daily activities and the change of habits related to health, among others (De Maeyer, Vanderplasschen, Lammertyn *et al.*, 2011; He *et al.*, 2011). These programmes are based on the assumption that response to treatment is a function of individual differences rather than a mere dose-response function (Padaiga, Subata & Vanagas, 2007). From this perspective it is not correct to speak about high or low doses, but rather adjusted or suitable doses which eliminate the need for (but not the possibility of) additional consumption. In general terms we can say that methadone maintenance treatments produce an immediate improvement in the quality of life which, however, does not increase sufficiently over time to reach that of the general population. It does not even reach the levels declared by patients with other serious psychopathological symptoms (Habrat, Chmielewska, Baran-Furga, Keszycka & Taracha, 2002; Karow *et al.*, 2011; Millson *et al.*, 2004; Nosyk, Marsh, Sun, Schechter & Anis, 2010; Nosyk *et al.*, 2011; Torrens, Domingo-Salvany, Alonso, Castillo & San, 1999), and, furthermore, the variables more closely linked to quality of life and the success of the programme are not associated with the drug itself but rather with psychosocial factors such as family support (Lina, Wu & Detels, 2011). The multiplicity of factors involved in

the severity of the addiction and the patient's self-perceived quality of life highlights the need to design programmes which attend to the many dimensions connected with the problem (Fernández Miranda, González García-Portilla, Sáiz Martínez, Gutiérrez Cienfuegos & Bobes García, 1999; Millson, *et al.*, 2006). And yet, quality of life is not one of the indicators used to measure the effectiveness of the treatments (Amato *et al.*, 2005; Fernández Miranda, 2000).

The repeated finding that high doses increase retention rates has been challenged by some authors, who find that the risk of abandonment is greater (1.3/1) when the dose exceeds 60 mg/day than with lower doses, with other factors predicting the success or failure of maintenance programmes (Mino, Page, Dumont & Broers, 1998). With regard to the consumption of non-prescription drugs, other studies also question the superiority of high dosage programmes, arguing that suitable psychosocial intervention accompanying low doses can obtain equal or better results than high doses (Banys, Tusel, Sees, Reilly & Delucchi, 1994). Contrary to the arguments proposed in favour of high dosage treatments, other studies have found that an increase in methadone doses above the adjusted levels can trigger a notable increase in craving and the consumption of heroin (Curran, Bolton, Wanigaratne & Smyth, 1999; Fareed *et al.*, 2010). Follow-up studies in the United States have shown that the minimum dose of methadone proposed by high dosage models (60 mg) is not considered necessary in clinical treatment, and that the growing trend among prescribing doctors is to take the opinions of the patients, rather than dosage policies, into account when establishing a suitable dose (D'Aunno, Folz-Murphy & Lin, 1999). Thus, listening to the patient in setting dosage improves results (Maddux, Desmond & Vogtsberger, 1995; Maddux, Prihoda & Vogtsberger, 1997). A study carried out in Spain with a representative national sample found that the average maintenance dose was 61.52 mg/day (SD = 49.14), which means that a large percentage of patients would have received doses below 60 mg/day (Roncero *et al.*, 2011). Other authors have found that the dosage is irrelevant in the achieving objectives and suggest that more attention should be paid to other aspects of the programme, such as interpersonal therapist-patient relationships (Blaney & Craig, 1999). Nevertheless, studies which explore variables related to doses lower than 90 mg/day are disappearing from the literature at the same time as guidelines are insistently recommending the prescription of high doses (D'Aunno, Pollack, Frimpong & Wuchiett, 2014).

Not many studies have attempted to discover patients' opinions, their perception of health in relation to the doses and the influence of their attitudes and other psychological variables in connection with the results of the treatment. A variety of studies report large discrepancies in the assessments of results as declared on the one hand by the professionals and perceived on the other by patients (Trujols *et al.*, 2013). While motivation is a key variable in achieving good treatment results independently of the dosage administered (Zeldman, Ryan & Fiscella, 2004), many studies concur in confirming that patients meet a variety of barriers to enter and remain in methadone maintenance programmes: the treatment they receive from the therapy team, being labelled "ill", long waiting times, the inflexibility in the prescription of the dosage, nondisclosure of the dosage received, the length of treatment, which is likely to be indefinite, the feeling that the dosage administered is too high, the lack of necessary participation in setting dosage levels, among others (e.g. Al-Tayyib & Koester, 2011; Deering *et al.*, 2011; Peterson *et al.*, 2010). Conversely, satisfaction with the treatment received, taking part in therapeutic activities, and the feeling that treatment has been beneficial are aspects which improve retention irrespective of the dosage received (Kelly, O'Grady, Brown, Mitchell & Schwartz, 2010; Montgomery, Sanning, Litvak & Peters, 2014; Vanderplasschen, Naert, Vander Laenen & De Maeyer, 2014). Satisfaction levels, therefore, are a more powerful predictor of retention than dosage levels (Kelly, O'Grady, Brown, Mitchell & Schwartz, 2011). The improvement in terms of quality of methadone maintenance treatments as biopsychological treatments with proven effectiveness and with adaptability to the different patient profiles and needs is an undeniable objective, as is the opinion of the patients themselves (Fernández Miranda, 2004; Rodríguez *et al.*, 2002).

The aim of the current study is to find empirical evidence which supports the use of high doses while taking the patient's perspective into consideration. To this end, the following hypotheses derived from the studies reviewed will be tested: (a) high doses are associated with higher self-perceived levels of quality of life; (b) the prescription of high doses corresponds to greater satisfaction with the treatment; (c) patients receiving high doses show lower levels of somatic and psychological distress; (d) high doses result in levels of cognitive performance equal to or better than low doses; (e) patients receiving high doses present reduced consumption of non-prescribed drugs in comparison to those on low doses. In addition, we attempt to discover the interactions between all these variables and the received dosage in a structural model which would suggest a causal hypothesis.

Method

Description of the health centres

The study was carried out on two samples, both obtained from specific public institutions: one from a large city (Madrid) and the other from small cities serving an urban and rural population (Extremadura). The Institute of Addiction is a public organism run under the auspices of Madrid City Council which attends to people with drug related problems or other addictive behaviours without the involvement of drugs in the Madrid city district (with a population of

approximately 3.2 million). The city is divided into seven sectors, each with its own Drug Addiction Centre (CAD), under the direct control of the public administration. In addition, there are three treatment centres (CCADs) run in conjunction with non-governmental organisations (Caritas and Red Cross) with public funding and independent management. These ten participating facilities have multidisciplinary treatment teams (doctors, nurses, psychologists, social workers, occupational therapists, and auxiliary staff). Patients may access these directly, on their own initiative, or through referral from other health services such as their general practitioner, mental health clinics or hospitals. The treatment provided is individualised, attending to the medical, psychological, occupational and social needs of each patient. In cases of active heroin consumption, a medical assessment and immediate initiation of methadone treatment may take priority, with the assessment of other aspects being delayed. Each centre has an Opioid Agonist Treatment Programme in which all professionals participate. The prescription of methadone or buprenorphine is at the discretion of the doctors, who are under no strict orders to follow dosage guidelines and can therefore prescribe the amounts they consider necessary based on their relationship with the patient and their own criteria. The patients have appointments with their doctors, as well as the other professionals, and can therefore describe their symptoms and state if they wish to raise or lower their doses, but the final decision as to dosage is taken by the medical professional and based on the characteristics and situation of the patient. The substance administered is methadone hydrochloride (there is a sub-programme with buprenorphine, which is not included in the present study) in solution or in tablet form, and take home doses are collected from the centre daily, twice a week or weekly.

The comparison sample (which we shall call sample B) was obtained from a variety of outpatient centres in Extremadura. These centres are run in a similar way to those in Madrid, but the population served in the small cities of Caceres and Badajoz (with 95.000 and 150.000 inhabitants respectively) and surrounding rural areas is noticeably different.

Participants

At the beginning of the study, a total of 1898 patients were receiving treatment in Madrid's 10 Institute of Addiction centres. These centres, serving Madrid city residents, are publicly financed and free for patients. For the present study, a maximum confidence interval of 4% was set (p=q=0.5), which required a sample of n = 450 individuals. The subjects were evaluated between January 2014 and January 2015, with a total of n = 538 cases, although after 80 cases were excluded on the grounds of errors in test completion or missing data, the final sample (sample A) was composed of n = 458 individuals. The criterion for inclusion was that patients needed to have been prescribed methadone for heroin addiction for at least 3 months in the corresponding centre. Exclusion criteria were: being diagnosed as dependent on a substance other than heroin, recent alcohol consumption, suffering from any kind of brain damage, acute psychotic symptomatology, receiving pharmaceutical treatment (antiretroviral or other) which would involve the modification of the methadone dosage, difficulties in understanding the Spanish language or any other which could jeopardise the adequate completion of the tests. Sample B was obtained in different public treatment centres in Extremadura. The total number receiving treatment at the start of the study was 100 individuals, with two thirds providing evaluations (n = 65). Despite this, the sample was representative, although with a higher margin of error (confidence interval of 7% for p=q=0.5).

Instruments

The World Health Organisation's Quality of Life Questionnaire, abbreviated version (*World Health Organization Quality of Life*, WHOQOL BREF; WHO, 2004), an instrument designed with the aim of providing a tool for the assessment of the quality of life applicable to all cultures. The full version consists of 100 items, while the short version, used here, has 26: two general questions (about the quality of life in general and satisfaction with health) and 24 items covering the four domains of physical, psychological, social and environmental health. Responses to the items are in the form of a five-point Likert type scale. Its psychometric properties have been analysed in transcultural studies (Skevington, Lotfy & O'Connell, 2004) and in the Spanish population (Lucas-Carrasco, 2012). The version used was provided by the Andalusian Health Service (2010). Internal consistency of the test in our sample was $\alpha = 0.89$, with a corrected item-test correlation of $0.30 < r_{it} < 0.63$.

The Methadone Treatment Satisfaction Scale, developed on the basis of the Verona Service Satisfaction Scale of 32 items (VSSS-32; Ruggeri *et al.*, 2000), validated in the Spanish clinical population (Trujols & Pérez de los Cobos, 2005), but modified to adapt it to the characteristics of the participating services (Appendix I). It consists of 13 items with five-option Likert type scales which evaluate aspects of treatment in general, and eight items asking whether specific type of care has been received, followed by an evaluation of such in the case of an affirmative response. In terms of scoring Treatment Satisfaction, the responses to the first 13 items are multiplied by 25, obtaining a scoring range of 0 to 100 points, with an average of 50. The internal consistency of the test was satisfactory, with $\alpha = 0.86$ for the 29 items and $\alpha = 0.91$ for the 13 first items, and a corrected item-test correlation of $0.70 < r_{it} < 0.88$.

Of the Symptoms Checklist-90 Revised (SCL-90-R, Derogatis, 1992), the Spanish version by González de Rivera *et al.* (1989) was used, with the analysis of it psychometric properties by De Las Cuevas *et al.* (1991). This is a questionnaire which asks the subject about the presence and intensity of 90 symptoms of psychological and psychosomatic distress,

scored on a Likert type scale from total absence (0) to maximum intensity (4). The theoretical items are grouped in nine scales, although the factor studies do not find that the items are grouped in these, representing rather symptoms of psychological distress both in the clinical population (De Las Cuevas *et al.*, 1991) and in the clinical population of substance abusers (Pedrero Pérez & López-Durán, 2005). It has three general indices: General Symptomatic Index (GSI, intensity of global psychological and psychosomatic suffering), Positive Symptoms Total (PST) and Positive Symptom Distress Index (PSDI, mean symptom intensity). In the present study, the SCL-90-R showed an internal consistency of $\alpha = 0.97$, with all items bar one (item 60) having a corrected item-test correlation of $0.30 < r_{it} < 0.71$.

Of the Montreal Cognitive Assessment scale (MoCA, Nasreddine et al, 2005), the Spanish version was used, proposed by the present authors and validated in the clinical population of substance abusers in Spain (Rojo-Mota, Pedrero-Pérez, Ruiz-Sánchez de León, Llanero-Luque & Puerta-García, 2013). This is a screening test which assesses ten cognitive domains using conventional neuropsychological tests which have been widely validated. The highest score is 30, although a weighting of two points is applied for individuals with less than nine years of schooling and one point for those with between 9 and 12 years of schooling (Chertkow, Nasreddine, Johns, Phillips & McHenry, 2011). Transcultural studies estimate a cut-off score of 26, with individuals at this level or higher being considered as performing normally, and lower scores suggesting cognitive deterioration or early dementia. The time required to administer the test is around ten minutes. The internal consistency of the test in the present study was $\alpha = 0.70$, with a corrected item-test correlation of $0.30 < r_{it} < 0.46$.

The ultraviolet-visible spectrophotometry method was used to determine the metabolites of opioids, cocaine, cannabis and benzodiazepines in urine. In the case of benzodiazepines, the result was considered positive only when none had been prescribed.

Clinical and sociodemographic data were obtained by consulting each subject's medical record. The time spent in the current programme was taken into account, as was age, sex, educational level and the methadone dosage prescribed at the time of assessment.

Procedure

The test administrators were given three training sessions before the assessment period began (one face-to-face session in the case of Extremadura), as well as ongoing support to resolve any doubts arising. Prior to the administration of the assessment protocol, posters in the dispensing offices announced the upcoming study and invited volunteers. Leaflets announcing the study were also distributed. From the start, patients were offered the possibility of taking part in the study when they came to the clinic to collect their doses (daily or weekly). If they did not have enough time on such occasions, they were offered the possibility of a scheduled appointment in the following days. A small percentage refused to participate (n = 70, 7%). Regarding the self-reports, the test administrator read out the questions and the patients signalled their responses on cards prepared with the different response types. The cognitive performance test was carried out *in situ* after the self-reports. If patients asked for a break, they were allowed to take one. The assessments took between 30 and 45 minutes, and was followed by the collection of a urine sample for toxicological analysis. Patients were told that a second sample would be taken one month later, independently of other samples routinely taken as part of their treatment. The completed protocols were sent by internal mail to the senior researcher who coordinated the data and configured the database. Badly completed protocols with missing data or unanswered questions (n = 80) were excluded. To study the connections with other variables the received dosage was considered as a linear variable, and the participants were also divided into groups, as follows: very low dosage (<30 mg/day), low dosage (30-59 mg/day), average dosage (60-90 mg/day) and high dosage (>90 mg/day).

All participants were provided with information about the objective of the tests and signed an informed consent form agreeing to anonymous use of the results. The study was approved by the ethical committees of Caceres and Badajoz.

Data Analysis

To compare categories χ^2_{gl} was applied. For comparisons between continuous variables, the Snedecor F_{gl} distribution was used by means of univariate and multivariate analysis. The proportion of variance explained by covariables was estimated by means of Wilks' lambda (λ). Linear and partial correlations were measured with Pearson's r. Stepwise linear regression analyses were carried out, and the proportion of explained variance (R^2) and the β coefficient reported. To measure effect size, the eta squared estimator was used (η^2, Cohen, 1973) and in order to interpret the results the rules of thumb suggested by the author (Cohen, 1988) were applied: small effect (0.01 - 0.06), moderate effect (0.06 - 0.13) and large effect (>0.13). For the category comparisons Cramer's V was applied as an estimator of effect size and for the mutual correlation coefficients (r^2). The statistical package SPSS 19 was used for all analyses except for η^2, which was calculated manually. The structural relationships between the variables was explored by means of the maximum verisimilitude method and the different models were compared through the quality of fit indices (ECVI, Hoelter), with subsequent application of absolute adjustment (χ^2 degrees of freedom), relative adjustment (CMIN/DF, RMSEA) and incremental adjustment (NFI, CFI, RFI, IFI, TLI), following the recommendations of Hooper, Coughlan and Mullen (2008), based on the information provided by the AMOS 18 software.

Results

Descriptive data

Table 1 shows the descriptive data for the main sample. The 4 to 1 ratio of men to women which can be observed is normal in all countries with a similar cultural background, and stable in time over decades. By sex, males have a significantly higher average age, although the effect size of these differences is insignificant (η^2= 0.01). There are also significant differences (albeit with similarly small effect size V = 0.003) in educational level, with women more frequently appearing in extreme groups (less than 9 or more than 15 years of schooling), while more than half of the males are found in the group with 9 to 12 years of schooling. There are no significant differences by sex in terms of prescribed methadone dosage (F_1 = 0.02; p = 0.89). There also appears to be no relation between prescribed dose and age of the patient (r = 0.06; p = 0.19), but there does seem to be one with the duration of treatment (r = 0.10; p < 0.05).

Sample B was composed of 57 men and 8 women, with an average age of 42,5 (SD = 7.1). With regard to years of schooling, 36.9% had less than 9 years, 44.6% between 9 and 12 years, 16.9% between 12 and 15 years, and 1.5% more than 15 years (there were no women in the last two categories, while 75% had less than 9 years of schooling).

Dosage

Doses smaller than 60 mg/day were received by 72.7% of the sample, with 37.3% taking less than 30 mg/day (M = 15.1; SD = 7.2) and 35.4% between 30 and 60 mg/day (M = 41.6; SD = 8.2). In terms of higher doses, 14.6% had between 60 and 90 mg/day (M = 73.1; SD = 9.7) and only 12.7% received more than 90 mg/day (M = 126.1; SD = 33.1).

Sample B had very different characteristics. Doses below 60 mg/day were received by 96.9%, with 78.5% taking less than 30 mg/day (M = 17.8; SD = 8.4) and 18.5% between 30 and 60 mg/día (M = 38.5; SD = 9.5). Between 60 and 90 mg/day was taken by 3.1% (M = 82.0; SD = 8.5) and nobody received more than 90 mg/day.

The relationship between dosage and self-perceived quality of life

The administered dosage correlated negatively and significantly with quality of life: in the physical domain (r = -0.24; p < 0.001; r^2 = 0.06), psychological (r = -0.14; p < 0.01; r^2 = 0.02), social (r = -0.10; p < 0.05; r^2= 0.01), environmental (r = -0.19; p < 0.001; r^2 = 0.04) and with the global score (r = -0.22; p < 0.001; r^2 = 0.05).

Table 2 shows the values obtained in the different domains of self-perceived quality of life by prescribed methadone dose. The scores demonstrated significant differences, both in the total quality of life score and in each of the domains, and always pointed to a worsening quality of life as doses increased. The effect size of these differences was low, but especially significant in the physical and environmental health domains, as well as in global quality of life. The *post hoc* tests revealed that the main differences between physical and environmental health were found among those who took very small doses and received a medium or high dosage; between extreme groups in the psychological domain; and between those who took very low doses and received a low dosage in the social relations domain.

Next, the possible effect of other variables on these differences was investigated. Neither sex (λ = 0.99; $F_{4;447}$ = 0.74; p = 0.56) nor length of time on the treatment programme (λ = 0.99; $F_{4;447}$ = 0.64; p = 0.63) explained a significant amount of the variance of the differences observed. The opposite was true however with age (λ = 0.98; $F_{4;447}$ = 2.47; p = 0.04; η^2 = 0.022) as well as educational level (λ = 0.96; $F_{4;447}$ = 5.13; p < 0.001; η^2 = 0.044). Age had a significant effect on the environmental (F_1 = 4.02; p < 0.05; η^2 = 0.009), and social

Table 1. *Descriptive data.*

	Men	Women	Total	*F*	*p*
n	364	94	458		
%	79.5	20.5			
Mean current age (SD) in years	47.6 (6.2)	46.1 (6.5)	47.3 (6.3)	3.97	‹ 0.05
Years of schooling	%			χ^2	*p*
‹ 9	28.8	36.2		9.1	‹ 0.05
9 - 12	51.1	34.0			
12 -15	16.5	24.5			
› 15	3.6	5.3			
				F	*p*
Mean dose (SD) in mg/day	47.4 (39.0)	45.7 (36.2)	47.0 (38.4)	0.14	0.71
Range	5 – 220	5 - 160	5 - 220		
Mean duration of treatment (SD) in months	93.3 (120.3)	89.5 (67.1)	92.5 (111.4)	0.09	0.77
Range in months	3 - 2011	3 - 281	3 - 2011		

domains ($F_1 = 7.86$; $p < 0.01$; $\eta^2 = 0.017$) as well as on the global score ($F_1 = 4.17$; $p < 0.05$; $\eta^2 = 0.009$), while educational level significantly affected the psychological and ($F_1 = 9.67$; $p < 0.01$; $\eta^2 = 0.021$) and environmental domains ($F_1 = 15.04$; $p < 0.001$; $\eta^2 = 0.032$), as well as the global score ($F_1 = 9.27$; $p < 0.01$; $\eta^2 = 0.020$). Controlling for educational level, age correlated significantly with social relations ($r = -0.13$; $p < 0.01$; $r^2 = 0.02$), with quality of environment ($r = -0.10$; $p < 0.05$; $r^2 = 0.01$) and with the global quality of life score ($r = -0.10$; $p < 0.05$; $r^2 = 0.01$); and controlling for age, educational level correlated significantly with psychological health ($r = 0.15$; $p < 0.01$; $r^2 = 0.02$), with quality of environment ($r = 0.19$; $p < 0.001$; $r^2 = 0.04$) and with the global score ($r = 0.15$; $p < 0.01$; $r^2 = 0.02$). Effect size was low in all cases.

On investigating the differences by prescribed dosage groups and controlling for variables previously showing interaction effects (age and educational level), significant differences appeared in all health domains (Table 2). While those receiving very low dosages (< 30 mg/day) displayed higher health levels, this went down among those groups receiving stronger doses. The effect size of these differences was moderate in the case of physical ($\eta^2 = 0.06$) and environmental health ($\eta^2 = 0.08$), as well as on the global quality of life score ($\eta^2 = 0.08$).

In sample B, dosage correlated negatively with quality of life and all its dimensions (physical, $r = -0.17$; psychological, $r = -0.23$; social $r = -0.07$; environmental health $r = -0.06$; and global score, $r = -0.16$), although statistical significance was not achieved in any of the cases.

The relationship between dosage/satisfaction and quality of life

The great majority (96.5%) declared that they were satisfied (50.2%) or very satisfied (46.3%) with the treatment they received, with only 3.5% declaring moderate dissatisfaction. There were no significant differences between the different groups in terms of prescribed methadone dosage ($F_3 = 1.94$; $p = 0.12$). When controlling for the effect of covariables, a significant relationship was found with sex ($F_7 = 5.43$; $p < 0.05$; $\eta^2 = 0.012$) and age ($F_7 = 10.86$; $p < 0.01$; $\eta^2 = 0.024$), but not with educational level nor duration of treatment. Women were found to be significantly more satisfied ($F_1 = 6.75$; $p < 0.05$; $\eta^2 = 0.015$) (M = 78.6; SD = 13.0) than men (M = 74.9; SD = 12.4). Age was negatively correlated with satisfaction ($r = -0.17$; $p < 0.001$; $r^2 = 0.03$), even when controlling for sex ($r = -0.16$; $p < 0.01$; $r^2 = 0.03$). When controlling for both variables, the differences among groups by dosage reached levels of significance, the lower the dosage of methadone administered, the higher satisfaction with treatment (Table 3).

Levels of satisfaction in sample B were similar: 96.9% were satisfied or very satisfied with their treatment. The satisfaction score correlated negatively with dosage ($r = -0.14$), without reaching statistical significance ($p = 0.27$).

The relationship between dosage and psychological distress

Table 4 shows that all the SCL-90-R indices display an increase parallel to the dosage of methadone prescribed. *Post hoc* tests revealed that only the group with the highest dosage manifested significant differences with the others, with more positive symptoms and a higher General Symptomatic Index. On investigating the possible effects of other variables on these differences, it was observed that only sex showed a significant interaction effect ($\lambda = 0.97$; $F_{3;448} = 2.47$; $p < 0.01$; $\eta^2 = 0.035$). This was not the case with age ($\lambda = 0.99$; $F_{3;448} = 2.21$; $p = 0.09$), educational level ($\lambda = 0.99$; $F_{3;448} = 2.12$; $p = 0.10$), nor duration of treatment ($\lambda = 0.99$; $F_{3;448} = 1.23$; $p = 0.30$). Women scored significantly higher than men in the three indices:

Table 2. *Quality of Life Domains (WHOQOL-BREF) and prescribed methadone dosage.*

	Dosage						
	very low	low	medium	high			(*)
WHOQOL	M (DT)				$F_{df=3}$	η^2	η^2
Physical health	24.35 (4.87)	23.15 (4.41)	22.28 (4.94)	20.98 (4.50)	8.63	0.054	0.055
Total	23.20 (4.79)						
Psychological health	18.96 (4.40)	18.62 (4.16)	18.52 (4.14)	17.05 (4.35)	2.94	0.019	0.042
Total	18.53 (4.30)						
Social health	9.19 (2.55)	8.41 (2.61)	8.64 (2.37)	8.21 (2.59)	3.52	0.023	0.041
Total	8.71 (2.57)						
Environmental health	26.52 (4.73)	25.35 (4.76)	24.54 (5.25)	23.62 (5.50)	6.17	0.039	0.077
Total	25.45 (5.00)						
Quality of life	79.01 (12.98)	75.53 (12.55)	73.99 (13.37)	69.86 (13.39)	8.05	0.051	0.075
Total	75.89 (13.24)						

Note. *Controlling for age and educational level (F df = 5).

General Symptomatic Index ($F_{gl=1}$ = 15.2; p < 0.001; η^2 = 0.032), Positive Symptoms Total ($F_{gl=1}$ = 8.3; p < 0.01; η^2 = 0.018) and Average Somatic Intensity ($F_{gl=1}$ = 14.5; p < 0.001; η^2 = 0.031). Table 4 shows that the relationship between dosage and distress is linear among males, but it is women taking medium-sized doses (60-90 mg/day) who present the highest indicators of distress.

A regression analysis was carried out of the SCL-90-R scores on the dosage of methadone received to investigate which symptom groups were linked to higher dosages. Among men, the Somatisation scale was the only one which displayed positive predictive capacity (R^2 = 0.06; β = 14.6), while among women this was the Phobic Anxiety scale (R^2 = 0.05; β = 13.6). When the same procedure was run with the SCL-90-R items (Table 5), models were found which explained a significant part of the dosage variance (12% in men, 17% in women), but none of the models were effective, generating excessive residues (Durbin-Watson < 1 in both cases).

In sample B, the dosage correlated negatively with all scales SCL-90-R and indices, without reaching statistical significance in any case.

The relationship between dosage and cognitive performance

Only 40% of the sample displayed normal cognitive performance (MoCA scores ≥ 26), while 41.5% presented mild cognitive impairment (between 21 and 25), and 18.5% were more severely affected (≤ 20). Taking the MoCA scores as a continuous variable, no differences were apparent between cognitive performance and dosage group ($F_{gl=3}$ = 1.96; p = 0.12), nor the effects of the variables sex ($F_{gl=1}$ = 0.00; p = 0.99), age ($F_{gl=1}$ = 0.08; p = 0.77) or duration of treatment ($F_{gl=1}$ = 0.57; p = 0.45). Educational level does not display any interaction effect when considering the corrected scores ($F_{gl=1}$ = 2.54; p = 0.11), while the opposite is the case with the uncorrected raw scores ($F_{gl=1}$ = 24.99; p < 0.001; η^2 = 0.055). However, when dosage is taken as a continuous variable, a significant and negative relationship is revealed between dosage and score obtained in the MoCA (r = -0.22; p < 0.001; r^2 = 0.05), which is maintained at the same levels when controlling for the remaining variables.

When subjects are classified according to performance on the MoCA (normal, mild and severe impairment), significant differences appear (Table 6). Only 25.9% of those taking more than 90 mg/day of methadone and 25.4% of those receiving 60-90 mg/day presented normal cognitive functioning, while this percentage rises to 50.3% for those taking very low doses and 40.1% for individuals receiving 30-60 mg/day doses.

In sample B, 32.3% of the subjects were found to have normal cognitive performance, while 50.8% had mild and 16.9% severe impairment. There was no significant corre-

Table 3. *Satisfaction with treatment scores by dosage of prescribed methadone, controlling for sex and age.*

	Dosage						
	very low	low	medium	high			
	M (DT)				$F_{gl=5}$	Sig.	η^2_p
Satisfaction	77.14 (12.89)	75.64 (11.65)	74.14 (13.25)	73.08 (13.05)	4.8	p< 0.001	0.051

Table 4. *SCL-90-R distress indices.*

	Dosage						
	very low	low	medium	high			
	M (SD)				$F_{gl=5}$	Sig.	η^2_p
General Symptomatic Index	0.75 (0.55)	0.785 (0.59)	0.91 (0.59)	1.10 (0.65)	5.93	p< 0.01	0.038
Positive Symptoms Total	35.74 (18.1)	37.60 (20.3)	42.93 (19.5)	47.66 (19.5)	6.83	p< 0.001	0.043
General Symptomatic Index	1.70 (0.59)	1.72 (0.53)	1.79 (0.54)	1.93 (0.57)	2.62	p= 0.51	0.017
	Men				$F_{gl=3}$	Sig.	η^2_p
General Symptomatic Index	0.71 (0.51)	0.73 (0.56)	0.79 (0.51)	1.10 (0.68)	6.13	p< 0.001	0.049
Positive Symptoms Total	34.7 (17.3)	36.4 (20.1)	39.9 (18.7)	47.3 (19.2)	5.58	p< 0.01	0. 044
General Symptomatic Index	1.68 (0.56)	1.64 (0.51)	1.68 (0.47)	1.93 (0.60)	3.28	p< 0.05	0.027
	Women				$F_{gl=3}$	Sig.	η^2_p
General Symptomatic Index	0.90 (0.65)	1.03 (0.67)	1.35 (0.69)	1.10 (0.57)	1.65	p= 0.18	0.052
Positive Symptoms Total	39.8 (20.6)	42.6 (20.9)	54.4 (18.5)	48.8 (16.2)	2.11	p= 0.10	0.066
General Symptomatic Index	1.80 (0.67)	2.02 (0.53)	2.17 (0.62)	1.93 (0.63)	1.48	p= 0.23	0.047

lation between the MoCA scores and the administered methadone dosage, neither was statistical significance found between these variables, not even when controlling for the remaining variables.

The relationship between dosage/consumption and non-prescribed substances.

At the time of assessment, 14.2% of subjects tested positive for opioids (other than methadone), 24.5% for cocaine, 34.9% for cannabis and 9.0% for non-prescribed benzodiazepines. One month or more after the assessment, 13.8% of those testing positive were for opioids, 23.1% for cocaine, 33.2% for cannabis and 9.6% for benzodiazepines. Taking both samplings, 81.9% of the subjects were heroin abstinent (8.3% tested positive on one occasion, and 9.8% in both), while 71.2% were cocaine abstinent (10.0% testing positive in one and 18.8. in both samplings), 60.0% were completely cannabis abstinent (11.8% were positive in one analysis, 28.2% in both), and 88.2% did not use non-prescribed benzodiazepines (5.0% found positive in one sampling and 6.8% in both). A total of 41.3% tested negative for all substances in both controls.

When dosage received was analysed, no significant differences were found (Table 7). Nor was there a significant difference between those testing positive for opioids when considering only the extreme groups with very low or very high doses in the first sampling ($\chi^2_1 = 3.56$; $p = 0.06$). However, the opposite was true in the second sampling ($\chi^2_1 = 5.96$; $p < 0.05$; $V = 0.02$), where positive results were significantly greater among those taking less than 30 mg/day than those on 90 mg/day of methadone. The number of subjects testing negative for opioids in both analyses was also greater in the high dosage group than in those taking less than 30 mg/day ($\chi^2_1 = 6.00$; $p < 0.05$; $V = 0.02$), in those taking between 30-60 mg/day ($\chi^2_1 = 6.00$; $p < 0.05$; $V = 0.02$) and among those subjects receiving 69-90 mg/day ($\chi^2_1 = 4.14$; $p < 0.05$; $V = 0.02$).

There was no significant difference in the case of the other drugs tested for in urine. Nor were significant differences found in relation to sex, years of schooling, duration of treatment or substances tested for.

In sample B, 27,7% were found to have traces of opioids other than methadone at the time of the assessment (26.2% in the second sampling), 27.7% had traces of cocaine (23.1% in the second test), 50.8% cannabis (same level in the follow-up test) and 15.4% benzodiazepines (13.8% in the later test). The proportion testing negative for all drugs en both samplings was 36.9%. No correlation with methadone dosage was found anywhere.

Structural model of the relationships between variables

Finally, on the basis of our results, various attempts were made to model the structural relationships between the different variables. The model achieving best fit (ECVI = 0.11; Hoelter = 914; p= 0.05) was that shown in Figure 1. All the indicators displayed a good fit to the data. ($\chi^2 = 6.3$; g.l. = 6; $p = 0.39$; CMIN/DF = 1.05; RMSEA = 0.01; NFI = 0.98; CFI = 0.99; RFI = 0.96; IFI = 0.99; TLI = 0.99).

Table 5. *SCL-90-R items with predictive capacity for methadone dosage.*

Ítem	Men	R^2x100	β
58	Heavy feelings in your arms and legs	4.67	5.96
75	Feeling nervous when you are left alone	2.99	8.54
12	Pains in heart or chest	1.32	5.35
24	Temper outbursts that you cannot control	1.65	-6.68
61	Feeling uneasy when people are watching or talking about you	1.52	5.07
	Women		
82	Feeling afraid you will faint in public	10.54	13.12
88	Never feeling close to another person	3.21	-9.75
33	Feeling fearful	2.86	6.58

Table 6. *Percentage of subjects by MoCA performance category and by methadone dosage.*

	Dosage					
	very low	low	medium	high		
MoCA	Percentage of subjects				χ^2_6	Sign.
Severe impairment	14.6%	19.1%	16.4%	31.0%	23.8	p< 0.01
Mild impairment	35.1%	40.7%	58.2%	43.1%		
Normal performance	50.3%	40.1%	25.4%	25.9%		

Discussion

Methadone maintenance is the therapy of choice in almost all cases in which a patient demands professional help for heroin addiction, but there are individual, pharmacological, social and cultural variables which can influence the way in which this treatment is provided. The objective of the present study is to explore the relationships between the methadone dosage administered and the range of associated variables; the final aim being to discover empirical evidence which can help prescribing doctors to provide the most suitable dosage.

The present study has found a linear relationship between higher prescribed methadone dosage and lower self-perceived quality of life, which affects all dimensions of subjective assessment. Especially those on doses above 60 mg/day estimate significantly lower levels of quality of life. The effect size of these differences was particularly significant both in the physical and environmental health domains, as in global quality of life. *Post hoc* analyses showed that the main differences in physical and environmental health were found between those taking very low and those receiving medium to high doses. In the psychological health domain, the main differences were in the extreme groups. When controlling for the remaining variables, the effect size of the differences was moderately high regarding the subjects' evaluation of environmental conditions, and also in quality of life as a whole.

Assessing the patients' satisfaction with their treatment is another way of evaluating the suitability of the programmes to their problems. Our results reveal an almost total overlap between the needs and expectations of the patients and the care offered by the specialised services participating in the study. Results exceed those obtained in the Spanish population in general regarding methadone treatment (Pérez de los Cobos *et al.*, 2004). Nevertheless, a negative relationship between dosage administered and degree of satisfaction is also found. These data appear to contradict the widespread belief that patients need higher doses than necessary in order to perceive the psychoactive effects of methadone. These results will be integrated below with those obtained for other variables.

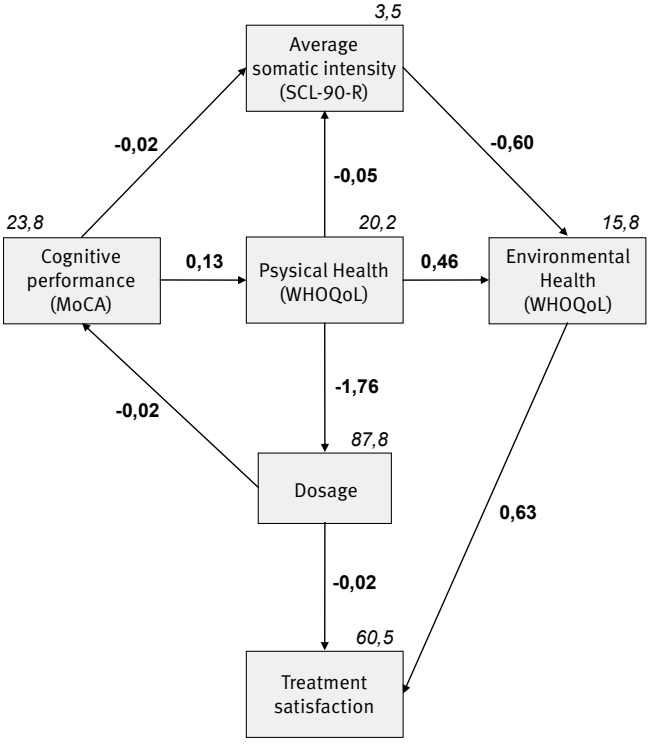

Figure 1. Structural model of the relationship between variables.

A linear relationship is also found between methadone dosage and psychological distress, especially in the case of people receiving high doses (>90 mg/day). Symptoms most frequently associated with such doses are of a somatic and indistinct character, or of anxiety in women. There does not seem to be a symptomatological pattern which fits specific

Table 7. *Percentage of positive toxicological tests for each drug. in relation to prescribed methadone dosage.*

	Dosage					
	very low	low	medium	high		
1st Sampling	% positives				χ^2_3	Sig.
Opioids	17.00	13.60	14.90	6.90	3.70	p= 0.30
Cocaine	21.60	26.50	26.90	24.10	1.33	p= 0.72
Cannabis	32.20	39.50	31.30	34.50	2.45	p= 0.48
Benzodiaz.	7.60	9.30	11.90	8.60	1.14	p= 0.77
2nd Sampling						
Opioids	15.80	16.00	11.90	3.40	6.70	p= 0.08
Cocaine	21.60	24.10	22.40	25.90	0.56	p= 0.91
Cannabis	31.60	36.40	34.30	27.60	1.82	p= 0.61
Benzodiaz.	6.40	11.10	11.90	12.10	3.23	p= 0.36

diagnostic categories, but rather a non-specific discomfort, as has been reported by prior studies (De Las Cuevas *et al.*, 1991; Pedrero Pérez & López-Durán, 2005). The question arises as to whether this discomfort is attributable to the side effects of methadone or rather to the fact that subjects experiencing greater levels of distress ask for higher doses of methadone to alleviate them. If the latter were the case, the results of the present study would point to the inefficacy of the method, which therefore makes it more likely that the discomfort is actually due to the increase in side effects accompanying increased doses of methadone. Nevertheless, the small effect size in almost all cases shows that the link between dosage and psychological distress is of little relevance.

Only 40% of patients were found to have normal cognitive functioning, according to the suggested cut-off points of the MoCA. This figure is lower than that obtained in studies using the same instrument with patients on high doses, which yielded 62% (Copersino *et al.*, 2012). Nevertheless, the figure is higher than that (29.1%) found in the same care context when subjects were assessed at the start of their treatment for addiction to a range of drugs (Rojo-Mota *et al.*, 2013). What these statistics suggest is that methadone maintenance improves the cognitive performance which could be expected at the base line, when factors such as the stress involved in drug consumption behaviour are relevant, but that treatment does not manage to raise the performance of a significant number of patients to population levels, not even to the levels of those who are completely abstinent of all opioids, including methadone, after a period of addiction (Darke *et al.*, 2012). Additionally, the mild cognitive impairment associated with methadone maintenance is linear with dosage, as the results of the present study indicates: around 40-50% on doses below 60 mg/day function normally, which is double the number of those taking more than 60 mg/day. There are no studies available to which these figures could be compared, mainly due to the fact that most programmes have adopted high dosage policies, ignoring the link between dosage and cognitive impairment in favour of other indicators.

As in all published research, a high percentage of subjects in methadone maintenance programmes persist in substance use. In the present study show, 60% tested positive for cocaine, cannabis or heroin when the assessment was carried out. Comparing results with other studies is difficult since the methods used vary, with self-reports of consumption frequently employed. Figures above 70% for consumption of any non-prescribed drugs in the previous month are reported in some cases, with 67% having used heroin in the previous week (Curran *et al.*, 1999). The current study cannot reflect the temporal dimension of consumption, given that drug use is only sampled at the time the assessment is administered. Nevertheless, figures found so far for the consumption of non-prescribed drugs are considerably higher than 60% (Darke *et al.*, 2012; Dobler-Mikola *et al.*, 2005).

Metabolites of opioids different to methadone were found in 18.1% of patients in both samplings. We can therefore consider that 80% of the patients sampled are not using heroin continuously or are abstinent. This figure is noticeably lower than that found in other studies, although the different methods used do not permit a perfect comparison (Keen, Oliver, Rowse & Mathers, 2003; Musshoff, Trafkowski, Lichtermann & Madea, 2010). What can clearly be observed, however, is that those receiving the highest dosage present significantly lower heroin consumption than those on doses below 90 mg/day. With regard to cocaine, no differences related to dosage were found. These results differ from those found in other studies, which revealed lower heroin and higher cocaine consumption at higher methadone doses, and the opposite at lower doses (Baumeister *et al.*, 2014).

While all indicators so far suggest that the lower the prescribed doses the better, the results regarding heroin consumption point in the opposite direction. The negative relationship between dose and risk of death from overdose is a repeated finding in earlier research (Liao *et al.*, 2013; Liu *et al.*, 2013; Van Ameijden *et al.*, 1999), but this is only confirmed when heroin is consumed by injection in addition to the administration of methadone. In such cases, the effects of both substances on the opioid receptors is cumulative, which does not happen when consumption is via inhalation or intranasal.

These results are worthy of reflection. Firstly, there appears to be no rationale for the prescription of high doses, other than in the case of persistent consumption of heroin by injection. In recent years we have seen certain institutions and research groups insistently proposing doses of around 100 mg/day, independently of variables other than mere opioid dependence (individual, environmental, therapeutic, etc.). To reach this conclusion, a host of studies were carried out which showed that certain indicators improved with a high dosage: rates of retention on the programmes, reduction of criminal activity, and reduction in the consumption of other drugs (Lingford-Hughes, Welch & Nutt, 2004). Nevertheless, far fewer studies have investigated variables relative to the patient, such as quality of life, satisfaction with treatment, returning to work, or relapse. When reviewing highest level research, not enough studies were found which explored the patient's perspective (Amato *et al.*, 2005; Fernández Miranda, 2001), and this is a rarity in the field of health care. Ignoring the perspectives and the opinions of the patient is unacceptable in any other health issue. The reasons for this contempt are to be found in the predominance of a model of the mental illness of addiction which converts an addict into a person who is unable to take appropriate decisions or make rational judgements because the brain has been taken hostage by the drug (Leshner, 1997). Some concerns have been voiced, however, with medical services being accused of enacting social control over

these patients, who are incapable of regulating their own behaviour. High-dosage policies have favoured the chronification of the disorder and its treatments, converting the patient into a mere recipient of the intervention (Harris & McElrath, 2012). Thus, stigmatisation is exacerbated and many people under treatment are forced to live in a state of sedation and powerlessness, with physical and psychological discomfort, and unable to participate actively in the day-to-day life of their community .

The model of mental illness has recently come under strong attack because none of its objectives are shown to have been met, while social stigmatisation is increased and the vast majority of substance dependent patients have had to endure doses which would only have made sense for the few cases of greatest severity (Hall, Carter & Forlini, 2015; Hammer *et al.*, 2013). The chemical blocking of receptors hands control to the physician and ignores treatments which could help the patients to regain control over their own behaviour. When the dosage does not cause lethargy, continued substance consumption or the success of the treatment are dependent on psychological variables (Senbanjo, Wolff, Marshall & Strang, 2009; Zeldman *et al.*, 2004), the patient's satisfaction with treatment is the best predictor of results (Kelly *et al.*, 2011), the results depend to a greater extent on the provision of psychosocial services as a complement to the pharmacological treatment (Mino *et al.*, 1998), certain psychotherapeutic interventions reduce the necessary dosage (Preston, Umbricht & Epstein, 2000), low doses are shown to be as useful as higher doses when combined with psychosocial treatments (Langendam, Van Brussel, Coutinho & Van Ameijden, 2001), and patients are able to self-administer their doses over and above the impositions of the programmes (Harris & Rhodes, 2013). Such an approach corresponds to an ethos of care where the focus is on recovery rather than medical/social control (White & Mojer-Torres, 2010).

As is common with similar research which has been consulted, our study has several limitations. It is impossible to attend to all variables involved in a treatment in a natural environment. Many patients, for example, though not all, receive psychoactive medicines as a complement to reduce psychopathological problems. These medicines may have positive or negative effects on the quality of life, satisfaction with treatment, and cognitive performance. While alcohol dependence has been controlled for, chronic alcohol consumption has not, and this can seriously interfere with cognitive performance (Chen *et al.*, 2011). The same applies to benzodiazepines, which were only controlled for when not prescribed, but could be taken in larger doses than those prescribed. In general, the consumption of substances other than methadone was restricted to the moment of assessment and a point one month later, but this does not report the intensity, chronicity, and variety of consumption patterns, although it is true that patients with proven dependence on any drug were excluded from the study. Treatments other than the purely medical (psychological, occupational, social and work integration, nursing care), are available to all participants, but not all make the same use of them nor stay on the treatments for the same amount of time and therefore the impact of each of these or the role they played in the results obtained cannot be quantified.

In conclusion, our data support the use of doses adjusted to the individual needs of each patient, via doctor-patient negotiation and a dynamic assessment of each case. With this approach, complete abstinence is not achieved, but neither is this the case in high-dosage programmes, as has been seen in the review of the literature, despite this being one of the strongest justifications for this kind of treatment, with its aim of achieving abstinence by a complete blocking of opioid receptors. Nevertheless, the consumption of non-prescribed substances is lower than in other studies, although it persists in the majority of cases. Self-perceived levels of quality of life are acceptable and at least comparable to those obtained in programmes with a different focus, although the fact of taking part in a treatment is a barrier to reaching the normal levels in the patients' normal environment. Patient satisfaction is scarcely improvable, thus indicating full acceptance of the individualised model aimed at recovery. The perception of physical health and the link to environmental health are essential in understanding the need for lower doses and satisfaction with the treatment received. Cognitive performance is unstable and negatively associated with dosage, and the repercussions of this on everyday life can lead to serious problems of integration. Reasons for recommending high doses are only apparent in those patients who persist in injecting heroin in order to reduce the likelihood of this type of consumption to the point of stabilisation. Future research should analyse in detail the role of each of the variables involved in the process of recovery and normalisation of the lives of these people. Quality programmes are needed which address not only the pharmacological issues related to addiction, but also the intrapersonal variables and environmental conditions which can favour the success of the programme and the normalisation of patients' lives, or conversely the breach of therapy and continuation of addiction. Methadone maintenance programmes should be oriented progressively towards individuals, valuing their opinions, encouraging their active participation in the process and improving the levels of quality of life, so that addressing their problems is done in the same way as in any other question of health.

Conflict of interest

The authors declare no conflict of interest.

Grupo MethaQoL: Madrid: Barreda Marina, M. A., Bartolomé Gil, C., Bosque Coro, S., Callejo Escobar, J., de Ema López, I., Dominguez Aranda, M. A., Ferrero Herreros, Y.

E., Galera García, Ó., Garrido Ureña, B., Gil de Bernabe Lopez, M. J., González Galnares, I. R., Gutiérrez Cáceres, S., Heras Dolader, S., Hernández Tejada, C., López Jiménez, M. C., López Zurita, C., Martin Carmona, G., Notario Poves, P., Olmos Espinosa, R., Pacheco Otoya, G., Pérez Carrasco, E., Pérez López, G., Puerta García, C., Rojo Mota, G., Sáez Maldonado, A., Salgado Marcos, N., San Juan Sanz, P., Sújar Plaza, M. I. Extremadura: Borrallo Berjón, M. J., Boticario Villarroel, M. V., Bueno Pozo, R., Iglesias Jiménez, M. F., Mateos Ayucar, M. P.

References

Adelson, M., Wilson, H. W., Celeste, V. Y., Linzy, S., Kreek, M. J. & Peles, E. (2013). Methadone maintenance treatment experience in Macao. Prospective follow-up for initial 4.5 years. *Journal of Psychoactive Drugs, 45*, 313-321. doi:10.1080/02791072.2013.825032

Al-Tayyib, A. & Koester, S. (2011). Injection drug users' experience with and attitudes toward methadone clinics in Denver, CO. *Journal of Substance Abuse Treatment, 41*, 30–36. doi:10.1016/j.jsat.2011.01.009

Amato, L., Davoli, M., Perucci, C. A., Ferri, M., Faggiano, F. & Mattick, R. P. (2005). An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Ttreatment, 28*, 321-329. doi:10.1016/j.jsat.2005.02.007

Banys, P., Tusel, D. J., Sees, K. L., Reilly, P. M. & Delucchi, K. L. (1994). Low (40 mg) versus high (80 mg) dose methadone in a 180-day heroin detoxification program. *Journal of Substance Abuse Treatment, 11*, 225-232. doi:10.1016/0740-5472(94)90079-5

Baumeister, M., Vogel, M., Dürsteler-MacFarland, K. M., Gerhard, U., Strasser, J., Walter, M., ... Petitjean, S. A. (2014). Association between methadone dose and concomitant cocaine use in methadone maintenance treatment: a register-based study. *Substance Abuse Treatment, Prevention, and Policy, 9*, 46. doi:10.1186/1747-597X-9-46

Benyamin, R, Trescot, A. M., Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., … Vallejo, R. (2008). Opioid complications and side effects. *Pain Physician, 11*, S105-S120.

Bell, J. & Zador, D. (2000). A risk-benefit analysis of methadone maintenance treatment. *Drug Safety, 22*, 179-190. doi:10.2165/00002018-200022030-00002

Bileviciute-Ljungar, I., Häglund, V., Carlsson, J. & von Heijne, A. (2014). Clinical and radiological findings in methadone-induced delayed leukoencephalopathy. *Journal of Rehabilitation Medicine, 46*, 828-830. doi:10.2340/16501977-1820

Blaney, T. & Craig, R. J. (1999). Methadone maintenance: does dose determine differences in outcome? *Journal of Substance Abuse Treatment, 16*, 221-228. doi:10.1016/S0740-5472(98)00031-2

Bourgois, P. (2000). Disciplining addictions: The bio-politics of methadone and heroin in the United States. *Culture, Medicine and Psychiatry, 24*, 165-195. doi:10.1023/A:1005574918294

Bracken, B. K., Trksak, G. H., Penetar, D. M., Tartarini W. L., Maywalt, M. A., Dorsey, C. M. & Lukas, S. E. (2012). Response inhibition and psychomotor speed during methadone maintenance: impact of treatment duration, dose, and sleep deprivation. *Drug and Alcohol Dependence, 125*, 132-139. doi:10.1016/j.drugalcdep.2012.04.004

Brugal, M. T., Domingo-Salvany, A., Puig, R., Barrio, G., García de Olalla, P. & de la Fuente, L. (2005). Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction, 100*, 981-989. doi:10.1111/j.1360-0443.2005.01089.x

Bourgois, P. (2000). Disciplining addictions: The bio-politics of methadone and heroin in the United States. *Culture, Medicine and Psychiatry, 24*, 165-195.

Chen, I. C., Chie W. C., Hwu, H. G., Chou, S. Y., Yeh, Y. C., Yu, C. Y. & Tan, H. K. L. (2011). Alcohol use problem among patients in methadone maintenance treatment in Taiwan. *Journal of Substance Abuse Treatment, 40*, 142-149. doi:10.1016/j.jsat.2010.09.004

Chertkow, H., Nasreddine, Z., Johns, E., Phillips, N. & McHenry, C. (2011). The Montreal Cognitive Assessment (MoCA): Validation of alternate forms and new recommendations for education corrections. *Alzheimer's & Dementia, 7*, S157. doi:10.1016/j.jalz.2011.05.423

Chugh, S. S., Socoteanu, C., Reinier, K., Waltz, J., Jui, J. & Gunson, K. (2008). A community-based evaluation of sudden death associated with therapeutic levels of methadone. *American Journal of Medicine, 121*, 66-71. doi:10.1016/j.amjmed.2007.10.009

Cohen, J. (1973). Eta-squared and partial eta-squared in fixed factor ANOVA designs. *Educational and Psychological Measurement, 33*, 107-112. doi:10.1177/001316447303300111

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2ª ed.)*. Hillsdale, NJ: Erlbaum.

Copersino, M. L., Schretlen, D. J., Fitzmaurice, G., Lukas, S. E., Faberman, J., Sokoloff, J. & Weiss, R. D. (2012). Effects of cognitive impairment on substance abuse treatment attendance: predictive validation of a brief cognitive screening measure. *American Journal of Drug and Alcohol Abuse, 38*, 246-250. doi:10.3109/00952990.2012.670866

Curran, H. V., Bolton, J., Wanigaratne, S. & Smyth, C. (1999). Additional methadone increases craving for heroin: a double-blind, placebocontrolled study of chronic opiate users receiving methadone substitution treatment. *Addiction, 94*, 665-674. doi:10.1046/j.1360-0443.1999.9456654.x

Darke, S., McDonald, S., Kaye, S. & Torok, M. (2012). Comparative patterns of cognitive performance

amongst opioid maintenance patients, abstinent opioid users and non-opioid users. *Drug and Alcohol Dependence, 126*, 309-315. doi:10.1016/j.drugalcdep.2012.05.032

D'Aunno, T., Folz-Murphy, N. & Lin, X. (1999). Changes in methadone treatment practices: results from a panel study, 1988-1995. *American Journal of Drug and Alcohol Abuse, 25*, 681-699. doi:10.1081/ADA-100101886

D'Aunno, T., Pollack, H. A., Frimpong, J. A. & Wuchiett, D. (2014). Evidence-based treatment for opioid disorders: A 23-year national study of methadone dose levels. *Journal of Substance Abuse Treatment, 47*, 245-250. doi:10.1016/j.jsat.2014.06.001

Deering, D., Sheridan, J., Sellman, J., Adamson, S., Pooley, S., Robertson, R. & Henderson, C. (2011). Consumer and treatment provider perspectives on reducing barriers to opioid substitution treatment and improving treatment attractiveness. *Addictive Behaviors, 36*, 636-642. doi:10.1016/j.addbeh.2011.01.004

De Las Cuevas, C., Gonzalez de Rivera, J. L., Henry Benitez, M., Monterrey, A. L., Rodriguez-Pulido, F. & Gracia Marco, R. (1991). Análisis factorial de la versión española del SCL-90-R en la población general. *Anales de Psiquiatria, 7*, 93-96.

De Maeyer, J., Vanderplasschen, W., Camfield, L., Vanheule, S., Sabbe, B. & Broekaert, E. (2011). A good quality of life under the influence of methadone: A qualitative study among opiate-dependent individuals. *International Journal of Nursing Studies, 48*, 1244-1257. doi:10.1016/j.ijnurstu.2011.03.009

De Maeyer, J., Vanderplasschen, W., Lammertyn, J., van Nieuwenhuizen, C., Sabbe, B. & Broekaert, E. (2011). Current quality of life and its determinants among opiate-dependent individuals five years after starting methadone treatment. *Quality of Life Research, 20*, 139-150. doi:10.1007/s11136-010-9732-3

Derogatis, L. R. (1992). *SCL-90-R: Administration, scoring and procedures manual for the R (evised) version and other instruments of the psychopathology rating scale series*. Towson: Clinical Psychometric Research.

Dobler-Mikola, A., Hattenschwiler, J., Meili, D., Beck, T., Boni, E., Modestin, J. (2005). Patterns of heroin, cocaine, and alcohol abuse during long-term methadone maintenance treatment. *Journal of Substance Abuse Treatment, 29*, 259-265. doi :10.1016/j.jsat.2005.08.002

Eiden, C., Leglis, Y., Clarivet, B., Blayac, J. P. & Peyrière, H. (2012). Co-morbidités psychiatriques associées à des fortes posologies de méthadone (>100 mg/j): analyse rétrospective d'une cohorte de patients traités. *Thérapie, 67*, 223-230. doi :10.2515/therapie/2012025

Faggiano, F., Vigna-Taglianti, F., Versino, E. & Lemma, P. (2003). Methadone maintenance at different dosages for opioid dependence. *Cochrane Database of Systematic Reviews, 3*, CD002208. doi:10.1002/14651858.CD002208

Fareed, A., Vayalapalli, S., Stout, S., Casarella, J., Drexler, K. & Bailey, S. P. (2010). Effect of methadone maintenance treatment on heroin craving, a literature review. *Journal of Addictive Diseases, 30*, 27-38. doi:10.1080/10550887.2010.531672

Farré, M., Mas, A., Torrens, M., Moreno, V. & Camí, J. (2002). Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug and Alcohol Dependence, 65*, 283-290. doi:10.1016/S0376-8716(01)00171-5

Fernández Miranda, J. J. (2001). Efectividad de los programas de mantenimiento con metadona. Una revisión de los resultados de los estudios de evaluación. *Medicina Clínica (Barcelona), 116*, 150-154.

Fernández Miranda, J. J. (2004). Calidad asistencial y cronicidad en los programas de mantenimiento con agonistas opiáceos. *Adicciones, 16*, 109-116.

Fernández Miranda, J. J., González García-Portilla, M. P., Sáiz Martínez, P.A., Gutiérrez Cienfuegos, E, Bobes García, J. (1999). Calidad de vida y severidad de la adicción en heroinómanos en mantenimiento prolongado con metadona. *Adicciones, 11*, 43-52.

González de Rivera, J. L., Derogatis, L. R., de las Cuevas, C., Gracia Marco, R., Rodríguez-Pulido, F., Henry-Benítez, M. & Monterrey, A. L. (1989). *The Spanish version of the SCL-90-R. Normative data in the general population.* Towson: Clinical Psychometric Research.

Grönbladh, L. & Öhlund, L. S. (2011). Self-reported differences in side-effects for 110 heroin addicts during opioid addiction and during methadone treatment. *Heroin Addiction and Related Clinical Problems, 13*, 5-12.

Gruber, S. A., Tzilos, G. K., Silveri, M. M., Pollack, M., Renshaw, P. F., Kaufman, M. J. & Yurgelun-Todd, D. A. (2006). Methadone maintenance improves cognitive performance after two months of treatment. *Experimental and Clinical Psychopharmacology, 14*, 157-164. doi:10.1037/1064-1297.14.2.157

Hall, W., Carter, A. & Forlini, C. (2015). The brain disease model of addiction: is it supported by the evidence and has it delivered on its promises? *Lancet Psychiatry, 2*, 105-110. doi:10.1016/S2215-0366(14)00126-6

Hammer, R., Dingel, M., Ostergren, J., Partridge, B., McCormick, J. & Koenig, B. A. (2013). Addiction: Current criticism of the brain disease paradigm. *American Journal of Bioethics Neuroscience, 4*, 27-32. doi:10.1080/21507740.2013.796328

Habrat, B., Chmielewska, K., Baran-Furga, H., Keszycka, B. & Taracha, E. (2002). Subjective Quality of Life in opiate-dependent patients before admission after six months and one-year participation in methadone program. *Przegl Lek, 59*, 351-354.

Harris, J. & McElrath, K. (2012). Methadone as social control: Institutionalized stigma and the prospect

of recovery. *Qualitative Health Research, 22*, 810–824. doi:10.1177/1049732311432718

Harris, M. & Rhodes, T. (2013). Methadone diversion as a protective strategy: the harm reduction potential of 'generous constraints'. *International Journal of Drug Policy, 24*, e43-e50. doi:10.1016/j.drugpo.2012.10.003

Hartgers, C., van den Hoek, A., Krijnen, P. & Coutinho, R. A. (1992). HIV prevalence and risk behavior among injecting drug users who participate in 'Low-Threshold' methadone programs in Amsterdam. *American Journal of Public Health, 82*, 547-551. doi:10.2105/AJPH.82.4.547

He, Q., Wang, X., Xia, Y., Mandel, J. S., Chen, A., Zhao, L., … Ling, L. (2011). New community-based methadone maintenance treatment programs in Guangdong, China, and their impact on patient quality of life. *Substance Use & Misuse, 46*, 749-757. doi:10.3109/10826084.2010.534124

Hooper, D., Coughlan, J. & Mullen, M. R. (2008). Structural equation modelling: Guidelines for determining model fit. Electronic *Journal of Business Research Methods, 6*, 53- 60.

Karow, A., Verthein, U., Pukrop, R., Reimer, J., Haasen, C., Krausz, M. & Schäfer, I. (2011). Quality of life profiles and changes in the course of maintenance treatment among 1,015 patients with severe opioid dependence. *Substance Use & Misuse, 46*, 705-715. doi:10.3109/10826084.2010.509854

Katz, N. (2005). The impact of opioids on the endocrine system. *Pain Management Rounds, 1*, 1-6. doi:10.1097/AJP.0b013e3181850df6

Keen, J., Oliver, P., Rowse, G. & Mathers, N. (2003). Does methadone maintenance treatment based on the new national guidelines work in a primary care setting? *British Journal of General Practice, 53*, 461-467.

Kelly, S. M., O'Grady, K. E., Brown, B. S., Mitchell, S. G. & Schwartz, R. P. (2010). The role of patient satisfaction in methadone treatment. *American Journal of Drug and Alcohol Abuse, 36*, 150–154. doi:10.3109/00952991003736371

Kelly, S. M., O'Grady, K. E., Brown, B. S., Mitchell, S. G. & Schwartz, R. P. (2011). Predictors of methadone treatment retention from a multi-site study: A survival analysis. *Drug & Alcohol Dependence, 117*, 170-175. doi:10.1016/j.drugalcdep.2011.01.008

Krantz, M. J., Kutinsky, I. B., Robertson, A. D. & Mehler, P. S. (2003). Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy, 23*, 802-805. doi:10.1592/phco.23.6.802.32186

Krantz, M. J., Martin, J., Stimmel, B., Mehta, D. & Haigney, M. C. P. (2009). QTc interval screening in methadone treatment. *Annals of Internal Medicine, 150*, 387-395. doi:10.7326/0003-4819-150-1-200903170-00104

Langendam, M. W., Van Brussel, G. H., Coutinho, R. A. & Van Ameijden, E. J. (2001). The impact of harm-reduction-based methadone treatment on mortality among heroin users. *American Journal of Public Health, 91*, 774-780. doi:10.2105/AJPH.91.5.774

Leavitt, S. B. (2003). Methadone dosing & safety in the treatment of opioid addiction. *Addiction Treatment Forum, 12*, 1-8.

Leshner, A. I. (1997). Addiction is a brain disease, and it matters. *Science, 278*, 45-47. doi:10.1126/science.278.5335.45

Liao, D. L., Chen, P. C., Chen, C. H., Hsieh, C. J., Huang, Y. F., Shih, W. Y. & Cheng, J. J. (2013). Higher methadone doses are associated with lower mortality in patients of opioid dependence in Taiwan. *Journal of Psychiatric Research, 47*, 1530-1534. doi:10.1016/j.jpsychires.2013.07.001

Lina, C., Wu, Z. & Detels, R. (2011). Family support, quality of life and concurrent substance use among methadone maintenance therapy clients in China. *Public Health, 125*, 269-274. doi:10.1016/j.puhe.2011.01.009

Lingford-Hughes, A. R., Welch, S. & Nutt, D. J. (2004). Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology, 18*, 293-336. doi:10.1177/0269881104048516

Liu, E., Rou, K., McGoogan, J. M., Pang, L., Cao, X., Wang, C., ... & Wu, Z. (2013). Factors associated with mortality of HIV-positive clients receiving methadone maintenance treatment in China. *Journal of Infectious Diseases, 208*, 442-453. doi:10.1093/infdis/jit163

Loeber, S., Kniest, A., Diehl, A., Mann, K. & Croissant, B. (2008). Neuropsychological functioning of opiate-dependent patients: A nonrandomized comparison of patients preferring either buprenorphine or methadone maintenance treatment. *American Journal of Drug and Alcohol Abuse, 34*, 584–593. doi:10.1080/00952990802308239

Lucas-Carrasco, R. (2012). The WHO quality of life (WHOQOL) questionnaire: Spanish development and validation studies. *Quality of Life Research, 21*, 161-165. doi:10.1007/s11136-011-9926-3

Maddux, J. F., Desmond, D. P. & Vogtsberger, K. N. (1995). Patient-regulated methadone dose and optional counseling in methadone maintenance. *American Journal on Addictions, 4*, 18-32. doi:10.1111/j.1521-0391.1995.tb00255.x

Maddux, J. F., Prihoda, T. J. & Vogtsberger, K. N. (1997). The relationship of methadone dose and other variables to outcomes of methadone maintenance. *American Journal on Addictions, 6*, 246–255. doi:10.1111/j.1521-0391.1997.tb00404.x

Maremmani, I., Pacini, M., Lubrano, S. & Lovrecic, M. (2003). When "enough" is still not "enough": effectiveness of high-dose methadone in the treatment of heroin

addiction. *Heroin Addiction & Related Clinical Problems, 5*, 17-32.

Mattick, R. P., Breen, C., Kimber, J. & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews, 3*, CD002209. doi:10.1002/14651858.CD002209.pub2

Maxwell, S. & Shinderman, M. (1999). Optimizing response to methadone maintenance treatment: use of higher-dose methadone. *Journal of Psychoactive Drugs, 31*, 95-102. doi:10.1080/02791072.1999.10471730

Millson, P., Challacombe, L., Villeneuve, P. J., Strike, C. J., Fischer, B., Myers, T., ... Hopkins, S. (2006). Determinants of health-related quality of life of opiate users at entry to low-threshold methadone programs. *European Addiction Research, 12*, 74-82. doi:10.1159/000090426

Millson, P. E., Challacombe, L., Villeneuve, P. J., Fischer, B., Strike, C. J., Myers, T., … Pearson, M. (2004). Self-perceived health among Canadian opiate users: a comparison to Canadian the general population and to other chronic disease populations. *Canadian Journal of Public Health, 95*, 99-103.

Millson, P., Challacombe, L., Villeneuve, P. J., Strike, C. J., Fischer, B., Myers, T., … Hopkins, S. (2007). Reduction in injection–related hiv risk after 6 months in a low-threshold methadone treatment program. *AIDS Education and Prevention, 19*, 124–136. doi:10.1521/aeap.2007.19.2.124

Mino, A., Page, D., Dumont, P. & Broers, B. (1998). Treatment failure and methadone dose in a public methadone maintenance treatment programme in Geneva. *Drug and Alcohol Dependence, 50*, 233-239. doi:10.1016/S0376-8716(98)00035-0

Mintzer, M. Z., Copersino, M. L. & Stitzer, M. L. (2005). Opioid abuse and cognitive performance. *Drug and Alcohol Dependence, 78*, 225–230. doi:10.1016/j.drugalcdep.2004.10.008

Mintzer, M. Z. & Stitzer, M. L. (2002). Cognitive impairment in methadone maintenance patients. *Drug and Alcohol Dependence, 67*, 41-51. doi:10.1016/S0376-8716(02)00013-3

Montgomery, L. T., Sanning, B., Litvak, N. & Peters, E. N. (2014). Preliminary findings on the association between clients' perceived helpfulness of substance abuse treatment and outcomes: Does race matter? *Drug and Alcohol Dependence, 139*, 152-158. doi:10.1016/j.drugalcdep.2014.03.026

Musshoff, F., Trafkowski, J., Lichtermann, D. & Madea, B. (2010). Comparison of urine results concerning co-consumption of illicit heroin and other drugs in heroin and methadone maintenance programs. *International Journal of Legal Medicine, 124*, 499-503. doi:10.1007/s00414-009-0361-8

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I.… Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*, 695-699. doi:10.1111/j.1532-5415.2005.53221.x

Nosyk, B., Guh, D. P., Sun, H., Oviedo-Joekes, E., Brissette, S., Marshd, D. C., … Anis, A. H. (2011). Health related quality of life trajectories of patients in opioid substitution treatment. *Drug and Alcohol Dependence, 118*, 259-264. doi:10.1016/j.drugalcdep.2011.04.003

Nosyk, B., Marsh, D. C., Sun, H., Schechter, M. T. & Anis, A. H. (2010). Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996–2006. *Journal of Substance Abuse Treatment, 39*, 22-31. doi:10.1016/j.jsat.2010.03.008

Notley, C., Blyth, A., Maskrey, V., Pinto, H. & Holland, R. (2015). Exploring the concepts of abstinence and recovery through the experiences of long-term opiate substitution clients. *Substance Abuse, 36*, 232-239. doi:10.1080/08897077.2014.941085

Pacini, M., Maremmani, A. G. I., Rovai, L., Rugani, F. & Maremmani, I. (2010). Treating heroin addicts. Blocking dosages and stimulation-stabilization of opioidergic system. *Heroin Addiction & Related Clinical Problems, 12*, 41-48.

Padaiga, Z., Subata, E. & Vanagas. G. (2007). Outpatient methadone maintenance treatment program. Quality of life and health of opioid-dependent persons in Lithuania. *Medicina (Kaunas), 4*, 235-241.

Pedrero Pérez, E. J. & López-Durán, A. (2005). Autoinformes de sintomatología depresiva en drogodependientes: nivel de coincidencia del BDI, SCL-90-R & MCMI-II. ¿Depresión o malestar inespecífico? *Adicciones, 17*, 215-230.

Pérez de los Cobos, J., Fidel, G., Escuder, G., Haro, G., Sánchez, N., Pascual, C.,… , Trujols, J. (2004). A satisfaction survey of opioid-dependent clients at methadone treatment centres in Spain. *Drug and Alcohol Dependence, 73*, 307-313. doi:10.1016/j.drugalcdep.2003.11.001

Perreault, M., Héroux, M. C., White, N. D., Lauzon, P., Mercier, C. & Rousseau, M. (2007). Treatment retention and evolution of clientele in a low threshold methadone substitution treatment program in Montreal. *Canadian Journal of Public Health, 98*, 33-36.

Peterson, J. A., Schwartz, R. P., Mitchell, S. G., Reisinger, H. S., Kelly, S. M., O'Grady, K. E.… Agar, M. H.. (2010). Why don't out-of-treatment individuals enter methadone treatment programmes? *International Journal of Drug Policy, 21*, 36-42. doi:10.1016/j.drugpo.2008.07.004

Preston, K. L., Umbricht, A. & Epstein, D. H. (2000). Methadone dose increase and abstinence reinforcement

for treatment of continued heroin use during methadone maintenance. *Archives of General Psychiatry, 57*, 395-404. doi:10.1001/archpsyc.57.4.395.

Rass, O., Kleykamp, B. A., Vandrey, R. G., Bigelow, G. E., Leoutsakos, J. M., Stitzer, M. L., … Mintzer, M. Z. (2014). Cognitive performance in methadone maintenance patients: effects of time relative to dosing and maintenance dose level. *Experimental and Clinical Psychopharmacology, 22*, 248-256. doi:10.1037/a0035712

Rodríguez, M., Jiménez-Lerma, J. M., Iraurgi, I., Murua, F., Bacigalupe, L., Chavarri, M. R., & Balsategi, B. (2002). Evaluación de la satisfacción con el tratamiento en un centro ambulatorio de drogodependencias a través del Treatment Perceptions Questionnaire (TPQ). *Adicciones, 14*, 1-8.

Rojo-Mota, G., Pedrero-Pérez, E. J., Ruiz-Sánchez de León, J. M., Llanero-Luque, M. & Puerta-García, C. (2013). Cribado neurocognitivo en adictos a sustancias: la evaluación cognitiva de Montreal. *Revista de Neurología, 56*, 129-136.

Roncero, C., Fuste, G., Barral, C., Rodríguez-Cintas, L, Martínez-Luna, N., Eiroa-Orosa, F. J., Casas, M, on behalf of the PROTEUS study investigators. (2011). Therapeutic management and comorbidities in opiate-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study. *Heroin Addiction and Related Clinical Problems, 13*, 5-16.

Roy, A. K., McCarthy, C., Kiernan, G., McGorrian, C., Keenan, E., Mahon, N. G. & Sweeney, B. (2012). Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. *Addiction, 107*, 1132-1139. doi:10.1111/j.1360-0443.2011.03767.x

Ruggeri, M., Lasalvia, A., Dall'Agnola, R., Van Wijngaarden, B., Knudsen, H.C., Leese, M., ... & The Epsilon Study Group (2000). Development, internal consistency and reliability of the Verona Service Satisfaction Scale - European Version. *British Journal of Psychiatry, 177*, s41-s48. doi:10.1192/bjp.177.39.s41

Schwartz, R. P., Highfield, D. A., Jaffe, J. H., Brady, J. V., Butler, C. B., Rouse, C. O., … Breteler, M. M. B. (2006). A randomized controlled trial of interim methadone maintenance. *Archives of General Psychiatry, 63*, 102-109. doi:10.1001/archpsyc.63.1.102.

Senbanjo, R., Wolff, K. I. M., Marshall, E & Strang, J. (2009). Persistence of heroin use despite methadone treatment: Poor coping self-efficacy predicts continued heroin use. *Drug and Alcohol Review, 28*, 608-615. doi:10.1111/j.1465-3362.2009.00064.x

Servicio Andaluz de Salud (2010). *Desarrollo de Programas de Tratamiento Asertivo Comunitario en Andalucía. Documento marco. Anexo 3.1.* Granada: Área de Dirección de Organizaciones Sanitarias de la Escuela Andaluza de Salud Pública.

Skevington, S. M., Lotfy, M. & O'Connell, K. A. (2004). The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Quality of life Research, 13*, 299-310. doi:10.1023/B:QURE.0000018486.91360.00

Skevington, S. M., Sartorius, N., Amir, M., and THE WHOQOL Group. (2004). Developing methods for assessing quality of life in different cultural settings. *Social Psychiatry and Psychiatric Epidemiology, 39*, 1-8. doi:10.1007/s00127-004-0700-5

Torrens, M., Castillo, C. & Perez-Sola, V. (1996). Retention in a low threshold methadone maintenance program. *Drug and Alcohol Dependence, 41*, 55-59. doi:10.1016/0376-8716(96)01230-6

Torrens, M., Domingo-Salvany, A., Alonso, J., Castillo, C. & San, L. (1999). Methadone and quality of life. *Lancet, 353*, 1101. doi:10.1016/S0140-6736(05)76462-X

Trujols, J., Portella, M. J., Iraurgi, I., Campins, M. J., Siñol, N. & Pérez de los Cobos, J. (2013). Patient-reported outcome measures: Are they patient-generated, patient-centred or patient-valued? *Journal of Mental Health, 22*, 555-562. doi:10.3109/09638237.2012.734653

Trujols, J. & Pérez de los Cobos, J. (2005). La perspectiva de los usuarios sobre los tratamientos de mantenimiento con metadona: una revisión centrada en la satisfacción con el tratamiento. *Adicciones, 17,* s181-s204.

Van Ameijden, E. J., Langendam, M. W. & Coutinho, R. A. (1999). Dose-effect relationship between overdose mortality and prescribed methadone dosage in low threshold maintenance programs. *Addictive Behaviours, 24*, 559-563. doi:10.1016/S0306-4603(98)00083-5

Vanderplasschen, W., Naert, J., Vander Laenen, F. & De Maeyer, J. (2015). Treatment satisfaction and quality of support in outpatient substitution treatment: opiate users' experiences and perspectives. *Drugs: education, prevention, and policy, 22*, 272-280. doi:10.3109/09687637.2014.981508

Verdejo, A., Toribio, I., Orozco, C., Puente, K. L. & Pérez-García, M. (2005). Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug and Alcohol Dependence, 78*, 283-288. doi:10.1016/j.drugalcdep.2004.11.006

Villeneuve, P. J., Challacombe, L., Strike, C. J., Myers, T., Fischer, B., Shore, R., Hopkins, S. & Millson, P. E. (2006). Change in health-related quality of life of opiate users in low-threshold methadone programs. *Journal of Substance Use, 11*, 137-149. doi:10.1080/14659890500256945

Walker, P. W., Klein, D. & Kasza, L. (2003). High dose methadone and ventricular arrhythmias: a report of three cases. *Pain, 103*, 321-324. doi:10.1016/S0304-3959(02)00461-X

Wang, P. W., Wu, H. C., Yen, C. N., Yeh, Y. C., Chung, K. S., Chang, H. C. & Yen C, F. (2012). Change in quality of

life and its predictors in heroin users receiving methadone maintenance treatment in Taiwan: An 18-month follow-up study. *American Journal of Drug and Alcohol Abuse, 38*, 213-219. doi:10.3109/00952990.2011.649222

Webster, L. R. (2013). Methadone side effects: Constipation, respiratory depression, sedation, sleep-disordered breathing, and the endocrine system. En Cruciani, R. A. & Knotkova H., *Handbook of Methadone Prescribing and Buprenorphine Therapy* (pp. 39-49). New York: Springer.

White, W. & Mojer-Torres, L. (2010). *Recovery-oriented methadone maintenance*. Chicago (IL): Great Lakes Addiction Technology Transfer Center, Philadelphia Department of Behavioral Health and Mental Retardation Services and Northeast Addiction Technology Transfer Center.

WHO (2004). *The World Health Organization Quality of Life (WHOQOL)-BREF World Health Organization*. Recuperado de http://www.who.int/substance_abuse/research_tools/whoqolbref/en/.

Zeldman, A., Ryan, R. M. & Fiscella, K. (2004). Motivation, autonomy support, and entity beliefs: Their role in methadone maintenance treatment. *Journal of Social and Clinical Psychology*, 23, 675-696. doi:10.1521/jscp.23.5.675.50744

Appendix I. *Satisfaction scale used.*

1. What is your general impression of the efficacy of the Drug Addiction Centre in dealing with your problems?
2. What is your general impression of the capacity of the professionals in the Drug Addiction Centre to listen to you and understand your problems?
3. What is your general impression of the behaviour of the Drug Addiction Centre staff and their personal treatment of you?
4. What is your general impression of the capacity of the Drug Addiction Centre staff to cooperate, when necessary, with your family doctor or other specialists?
5. What is your general impression of the all the services that you have received in the Drug Addiction Centre?
6. What is your general impression of the efficacy of the centre in helping you improve your relationship with your closest relatives?
7. What is your general impression of the efficacy of the centre in helping your closest relatives to find out about and understand your problems better?
8. What is your general impression of the Drug Addiction Centre staff's knowledge of your problems, past and present?
9. What is your general impression of the information you have received about your diagnosis and the possible development of your addiction?
10. What is your general impression of the efficacy of the centre in helping you to improve your relationships with people outside your family environment (friends, neighbours, workmates)?
11. What is your general impression of the clarity and precision of the instructions received about what you had to do between appointments?
12. What is your general impression of the efficacy of the centre in helping you to improve your ability to look after yourself (e.g. personal hygiene, diet, accommodation, etc.)?
13. What is your general impression of the help you have received when suffering side-effects and discomfort caused by your medicines?

Response options: 1 Very bad; 2 Generally unsatisfactory; 3 Not bad, not good; 4 Generally satisfactory; 5 Excellent.