Perceived stress related to methadone withdrawal

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Abstract

Background: Stress is a known risk factor in addiction relapse, and prior studies show that relapse induced by stress may be more likely than drug-cue induced relapse. The main goal of our research was to establish the influence of perceived stress in methadone withdrawal outcome and the psychological factors involved. **Method:** A sample of 81 methadone maintenance treatment outpatients was evaluated and then observed during methadone dose reduction. Results: a multivariate analysis first showed that successful detoxification was predicted by perceived stress, patient-clinic staff agreement, pharmacotherapy support and social care; and second, perceived stress was predicted by anxiety, depression, self-control, social care and benzodiazepine use. Conclusions: These findings suggest that high levels of stress could increase the risk of failure in methadone detoxification, so a clinical intervention on the psychological factors related to stress would be indicated to improve effectiveness of methadone withdrawal treatment.

Keywords: Methadone, detoxification, stress, self-control, social support.

Resumen

Estrés percibido relacionado con la retirada de metadona.
Antecedentes: el estrés es un conocido factor de riesgo de recaída de la adicción y estudios anteriores muestran que puede ser mayor la probabilidad de recaída ante respuestas de estrés que ante estímulos asociados al consumo de drogas. El objetivo de nuestra investigación fue averiguar la influencia del estrés percibido en el resultado de la retirada de metadona y su relación con los procesos psicológicos implicados. **Método:** 81 pacientes ambulatorios en tratamiento de mantenimiento con metadona fueron evaluados y posteriormente observados durante la reducción de dosis de metadona. **Resultados:** el análisis multivariante mostró en primer lugar, como predictores del éxito de la desintoxicación, al grupo compuesto por estrés percibido, acuerdo paciente-facultativos, tratamientos farmacológicos complementarios y atención social; en segundo lugar, como predictores del estrés percibido, al conjunto de factores de ansiedad, depresión, autocontrol, apoyo social y consumo de benzodiacepinas. **Conclusiones:** los resultados sugieren que niveles altos de estrés podrían incrementar el riesgo de fracaso en la desintoxicación, por lo que una intervención clínica sobre los procesos psicológicos relacionados con el estrés resultaría indicada para mejorar la efectividad del tratamiento de retirada de metadona.

Palabras clave: metadona, desintoxicación, estrés, autocontrol, apoyo social.

During a methadone maintenance treatment (MMT) for opioid addiction, in particular in the final stage, patients may be exposed to stress situations. Stressful life events often need adaptive responses by the patients that challenge existing coping skills, in particular when situations are considered harmful, threatening or challenging.

Two significant contributions in psychology related to coping-stress are particularly relevant to this study: Lazarus and Folkman (1986) stated that coping can influence the frequency, severity, duration and form of neurochemical reactions to stress, understanding that the coping method reflects people's ability to manage a situation and depending on the resources they have available, their skills to use them and the limitations hindering the use of these resources. Ribes (2008) expressed that biological modulation by contingencies is one of the psychological health model process factors and explains that, in the same way as biological functions can regulate the behavior of an individual, behavior can modulate the biological reaction in stressful situations. Lazarus and Folkman and Ribes related the behavior that modulates biological reactivity with the effective competences available and the functional capacity deployed in the organism-environment interaction. Also from both viewpoints (cognitive-behavioral and interbehavioral), it has been thought that the way in which persons behave in stressful situations can affect their vulnerability state and consequently, their health.

Stress is a well-known risk factor in the development of addiction and relapse vulnerability induced by stress is even more relevant than drug-cue induced relapse (Hyman, Paliwal, & Sinha, 2007; Leri, Tremblay, Sorge, & Stewart, 2004), so in stressful situations, the lack of effective coping can lead detoxified and drug-abstinent patients to experience a compulsive drug-seeking state. Furthermore, stress is associated with anxiety, depression, irritability, fear, etc. (Goeders, 2004; Sinha, 2001), as well as with

psychological responses related to Grade I methadone withdrawal symptoms that can even continue for a long time after achieving zero-dose (Kanof, Aronson, & Ness, 1993; Wermuth & Brummet, 1987). Therefore, methadone withdrawal itself involves a situation with a high probability of experiencing stress for patients ending a maintenance treatment. Besides, when the zero-dose of methadone is achieved after a long—sometimes very long—maintenance period, demand level and adaptation difficulties are increased in patients who have managed to overcome the detoxification barrier. Milby et al. (1994) referred to this as "detoxification phobia", an emotional disorder that may be a predictor of discontinuing methadone withdrawal, associated on the one hand, with the occurrence of withdrawal symptoms during dose reduction and, on the other hand, with posttreatment relapses due to patients' mistrust of their own ability to maintain drug abstinence. These authors' conclusions are consistent with the findings of Reilly et al. (1995) in a study on perceived self-efficacy in patients during methadone maintenance treatment following a detoxification protocol. These authors defined self-efficacy as people's confidence in their own skills to prevent opioid consumption in risk situations. They measured self-efficacy during maintenance treatment and during methadone reduction. Results indicated that the self-efficacy level increased progressively from the start of the maintenance treatment and continued along the stabilization phase until the start of the methadone dose reduction, when self-efficacy level decreased to that of the first months of dose stabilization.

The above studies suggest that some stress-associated factors, such as affective states and/or the competence level of patients on MMT may be present in the methadone detoxification process when patients are undergoing such interventions. The main goal of our study was to establish whether this relationship can be found in Spanish population, in opioid-dependent patients on MMT before starting methadone withdrawal, as well as whether some stress predictors could be established that allowed for future planning of adequate psychotherapeutic procedures that would contribute to the success of detoxification and lasting abstinence during posttreatment. Based on clinical experience, we expected that, in addition to emotional and competence factors, other psychological variables, such as drug abuse, use of benzodiazepines and a non-socially adjusted lifestyle, would be also related to a higher perception of stress in patients starting the methadone withdrawal process.

Method

Participants

Eighty-one outpatients from 16 clinics from the Region of Madrid participated in a cohort study performed between 2007 and 2009. The mean age was 41.76 years (SD = 6.35; range: 27.51 - 60.69), distributed as follows: 74.1% men and 26.9% women; 49.4% were single and 30.8% married or with a partner; 44.4% lived with their family of origin and 27.2% with their own family; 29.6% had primary education, 35.8% secondary education, and 23.5% high school or an equivalent education; 48.2% of the participants were employed, 27.2% were unemployed at that time, and 16% received work disability; 80.2% had no legal incidents when the study was started. Clinically, 56.8% of the patients had positive markers for HCV, 27.2% for HIV and 13.6% for HBV; 16% of them had no biological diseases, and 18.5% had been

diagnosed with dual pathology; 39.4% followed some type of drug therapy due to biomedical conditions and, with regard to psychoactive drugs, 38.3% were treated with benzodiazepines, 16% with antidepressants, 4.9% with antipsychotics, and 1.2% with anticonvulsants. The mean age at onset of heroin use was around 20.3 years (SD = 5.21; range: 11 - 35) and the mean addiction time 17.68 years (SD = 5.84; range: 2.32 - 32.10). The participants reported abstinence from heroin (73.4%), and cocaine (65.8%) during the 6 months prior to inclusion in the study, and from cannabis (62%) and alcohol (37.7%) during the previous 3 months.

Instruments

- Questionnaire adapted from Carreras (2007) to inquire about social, demographic and clinic variables, drug abuse and characteristics of methadone maintenance treatment.
- *Perceived Stress Scale* (short version) (*PSS-10*; Cohen, Kamark, & Mermelstein, 1983). This instrument evaluates the level of perceived stress during the last month. The 10-item version provides a reliable and valid measure of perceived stress for use where a short scale is required (Remor, 2006). The questionnaire consists of 10 items with a 5-point response scale ranging from 0 (*never*) to 4 (*very often*). The total score of the PSS-10 is obtained by reversing the scores of Items 4, 5, 6 and 7 and subsequently adding the 10 items' scores. A higher score indicates a higher level of perceived stress. Cronbach's alpha coefficient for the PSS-10 in the current sample was .88.
- *Hospital Anxiety and Depression Scale* (*HADS*; Zigmond & Snaith, 1983). This scale is composed of 14 items divided into two subscales with 7 items each, evaluating Anxiety (HADS-A) and Depression (HADS-D), respectively. The scale is a self-administered instrument with a 4-point Likert-type scale (0 to 3). Some items (1, 3, 5, 6, 8, 10, 11, and 13) scores need reversing. Cronbach's alpha coefficient for the HADS-A in the current sample was .81 and .86 for the HADS-D.
- *Oviedo Sleep Questionnaire* (*OSQ*; Bobes et al., 2000). This is a brief semistructured interview for performing the DSM-IV and ED-10 diagnoses of insomnia and hypersomnia. For this study, we used only the insomnia subscale of the instrument, composed of 9 items in a 5-points scale (1 to 5; range: 9 - 45). Cronbach's alpha coefficient for the insomnia subscale in the current sample was .88.
- *Psychosocial Interaction Variables Questionnaire* (*PIV*; Pedrero, Pérez-López, De Enea, & Garrido, 2005). This was designed to assess competences and was validated in Spanish drug-addicted population. It is composed of 84 items with a 4-point response scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*). The items are divided into nine subscales: Self-control (11), Self-efficacy (9), Problem-focused coping (11), Emotion-focused coping (recoded to make its sign equivalent to the other skill variables) (12), Social support (5), Social skills (10), *Locus* of control (3), Optimism (11) and Self-concept (12). Partial scores of the PIV subscales are obtained by tabulating items to + 2, + 1, -1, -2. Items left blank or double-marks are scored with 0. A higher score indicates a higher level of competences. Cronbach's alpha coefficient for the total PIV in the current

sample was .94 and the subscales ranged from .72 (locus of control) to .83 (Self-concept).

– Data from the clinical histories about the evolution of patients on MMT and during the dose reduction process were entered in the report of each patient with their consent.

Procedure

The sample was selected from a reference population of 2,710 patients on MMT who were undergoing withdrawal treatment from the start of the study and who according to the inclusion criteria, were adult men and women with a diagnosis of opioid dependence. Patients undergoing methadone detoxification on an urgent basis or for some type of administrative penalty were excluded; detoxification procedures shorter than one month were not considered either. As a result, the target population was composed of 148 patients. For this study only the 89 patients who previously signed informed consent and completed assessment instruments were selected. After excluding the cases with missing responses, 81 participants composed the final sample.

The 81 participants were included in to the study by order of arrival at each respective site, as the starting condition of methadone detoxification occurred. The detoxification procedure used in all cases was the gradual dose reduction, with pharmacotherapy support in 28% of cases, mainly symptomatic therapy (benzodiazepines and antidepressants) and alcohol interdictors (disulfiram). The average dose of methadone at the beginning of detoxification was 55.58 mg. (SD = 38.15; range: 11 - 230). The occurrence of other procedures during detoxification was also registered, such as individual psychotherapy, which took place in 43.5% of cases and/or social care, in 33%. The particular characteristics of the psychotherapeutic treatment undertaken and the specifics of social care were not recorded for this study.

Having achieved the goal of zero-dose, 43.80% of the participants continued in conventional drug-free treatments; 47% did not follow specific treatments but underwent a MMT follow-up ranging from one to six months; the remaining 9.20% were lost to follow-up.

The observation period for each patient ranged from the inclusion in the study to discontinuation, either by relapse during detoxification or by reaching the zero-dose, the latter considered in this study as the success criterion. The main detoxification time in relapsed participants was 428.21 days (SE = 52.63; 95% CI: 325.06 - 531.37). In patients who managed to reach zero-dose of methadone, it was 469.81 days (SE = 52.76, 95% CI [573.23, 366.40]. Patients observed after achieving zero-dose were able to maintain abstinence for an average of 516.24 days (SE = 60.43; 95% CI [397.80, 634.68], and the greatest impact of relapses took place between 20 and 24 months after reaching zero-dose of methadone.

Data analysis

Descriptive data. The arithmetic means, standard deviations and relative and absolute frequencies were calculated for variables related to the personal characteristics of the participants, the methadone maintenance treatment conditions they had followed at their respective sites and the evolution of methadone withdrawal treatment they had underwent. Finally, descriptive data were obtained from methadone withdrawal outcomes, in terms of reaching zero-dose and posttreatment evolution.

Survival analysis. This procedure was used to estimate the participation time period of patients in the study at the two observed moments: achieving zero-dose of methadone and abstinence during posttreatment. Each participant was followed-up for a certain period of time (which was different for each case), from the initial event (starting dose of methadone reduction) until the terminal event (detoxification interruption or relapse after zero-dose) or until the end of the study. The monitoring period ended when a terminal event was shown by the participants. One terminal event in each analysis was considered. As a result, three analyses were performed considering three possible terminal events: zero-dose, detoxification interruption and relapse during posttreatment.

Multivariate analysis. In the inferential level of analysis, a logistic regression model was first built to establish the predictors of success in reaching zero-dose of methadone. The variables that were significant according to a previous bivariate analysis were entered in the model. A second linear regression procedure was applied to investigate more precisely the perceived stress predictors, starting from different psychological variables related significantly to this factor. The variables that had exceeded the cut-off point ($p \leq .15$) were entered in the multiple regression equation by the forward entry method. The analyses were performed with the software SPSS-18.0.

Results

Methadone withdrawal treatment outcomes

Fifty-eight percent of the patients undergoing methadone withdrawal treatment discontinued the process before achieving zero-dose and 11% had a relapse in the months following detoxification. However, 28% of the study participants had a successful detoxification and were able to remain abstinent for up to six months after methadone withdrawal; 3% of the patients could not be observed during the posttreatment period.

Factors associated with zero-dose of methadone

Bivariate analysis showed a successful detoxification relationship with anxiety (t = 2.10, p = .04, d = -.49), perceived stress (t = 3.20, p = .002, d = -.75), MMT permanence (t = 3.30, p = .001, d = -.73), initial dose reduction (t = 2.11, p = .04, d = -.49), opioid withdrawal symptoms (t = -2.63, p = .01, d = .62), psychological management (χ^2 = 5.55, p = .02), employment counseling service (χ^2 = 4.23, p = .04), frequency of employment counseling service (χ^2 = 7.31, p = .03), detoxification treatment compliance (χ^2 = 8.79, p = .003), interdisciplinary assessment (χ^2 = 5.36, p = .02), patient-clinic staff agreement (χ^2 = 10.02, p = .002), pharmacotherapy support (χ^2 = 11.94, p = .001), social care (χ^2 = 6.98, p = .008), heroin use (χ^2 =5.63, p = .02), and cocaine use (χ^2 =10.06, p = .002).

Predictors of zero-dose of methadone

The inferential data analysis allowed relating the methadone withdrawal outcome in detoxification stage (zero-dose as dependent variable) with the other variables examined. The posttreatment evolution could not be analyzed due to reduced sample size of patients with successful detoxification. The final equation, containing the next set of four variables: pharmacotherapy

support (OR = 23.81, *p* = .001), social care (OR = 12.89, *p* = .002), patient-clinic staff agreement (OR = 12.29, *p* = .02) and perceived stress (OR = .87, *p* = .005), accounted for 59% of the variance on methadone zero-dose achievement (R^2 = .59). The first three variables appeared as protection factors, and stress as a risk factor for the success of detoxification. Predictive validity of the four-variable model was supported by sensitivity and specificity (*Se* = 85.8%, *Sp* = 78.1%) and the ROC curve (AUC= .90, 95% CI: .82 - .97), offering a 90% power of prediction according to participants' achievement of zero-dose. This model complied with the criteria of normality, linearity, no co-linearity and sample size.

Factors associated with perceived stress

A first simple linear regression analysis showed the relationship of perceived stress as a dependent variable related to personal variables with the affective states of anxiety, depression and insomnia; with the competences of self-efficacy, self-control, self-concept, optimism, social skills, problem-focused coping, emotion-focused coping and social support; with heroin, cocaine and benzodiazepine use (prescribed and/or self-administered); and with lifestyle (consisting of living in family, having an employment, having no current legal incidents, and heroin and cocaine abstinence in the past 6 and 3 months, respectively). The coefficients and significance tests are shown in Table 1.

Predictors of perceived stress

Upon constructing a multiple linear regression model from all these variables, the equation was obtained formed by the group: anxiety, depression, self-control, social support and use of benzodiazepines, as better predictors of perceived stress. The model coefficients, standard errors, significance tests and confidence intervals are included in Table 2.

Table 1
Simple linear regression analysis. Dependent variable: perceived stress. Cut-off point, p≤0.15

Variables	B	t	p	95% confidence interval for *B*
Anxiety	1.85	9.17	.00	1.46 to 2.27
Depression	1.28	7.96	.00	.92 to 1.53
Insomnia	.41	4.26	.00	.22 to 0.60
Self-concept	-.12	-5.08	.00	-.17 to -0.07
Self-efficacy	-.11	-3.55	.001	-.18 to -0.05
Optimism	-.13	-4.67	.00	-.18 to -0.07
Locus Control	-.02	-1.15	.26	-.06 to 0.02
Social skills	-.06	-2.17	.03	-.11 to -0.00
Emotion coping	-.12	-4.99	.00	-.17 to -0.07
Problem coping	-.15	-4.57	.00	-.21 to -0.08
Social support	-.04	-2.02	.05	-.08 to -0.00
Self-control	-.17	-7.60	.00	-.22 to -0.13
Use of heroin	3.40	1.67	.10	-.65 to 7.46
Use of cocaine	4.03	2.13	.04	.26 to 7.80
Use of cannabis	.82	.43	.67	-2.98 to 4.62
Alcohol intake	-1.72	-.89	.38	-5.58 to 2.14
Benzodiazepine use	6.66	3.79	.00	3.16 to 10.16
Lifestyle	-1.98	-2.89	.005	-3.34 to -0.62

Table 2
Multiple linear regression model. Dependent variable: perceived stress

Predictors	Non-standardized coefficients	Standardized coefficients				95% confidence interval for *B*	
	B	SE B	β	t	p	Lower limit	Upper limit
(Constant)	6.54	1.74		3.75	.00	3.06	10.02
Anxiety	.79	.23	.31	3.42	.001	.33	1.25
Depression	.45	.17	.24	2.62	.01	.11	.78
Self-control	-.08	.02	-.32	-3.92	.00	-.13	-.04
Social support	-.04	.01	-.19	-3.01	.004	-.06	-.01
Benzodiazepine use	4.15	1.10	.24	3.79	.00	1.97	6.34

Findings showed a higher level of perceived stress when higher scores in anxiety and depression HAD subscales were obtained by patients. Self-control and social support had an inverse relationship with perceived stress, indicating that high levels of these competences reduced the stress level perceived by the patients. Finally, the model indicated that patients using benzodiazepines before undergoing methadone reduction had a higher perceived stress level than patients without this psychoactive drug use. The five-predictor model accounted for 72% of the variance of perceived stress (R^2 = .72) and complied with the criteria of normality (K-S: *p* = .20; S-W: *p* = .12), linearity, sample size, no co-linearity, homogeneity and independence.

Discussion

Psychological factors related to methadone withdrawal in MMT outpatients indicated perceived stress as one of predictors for reaching zero-dose, a relationship with no empirical evidence to date. Regarding to affective states, an association had been previously established with anxiety, depression and post-traumatic stress (Latowsky, 1996; Milby et al., 1994), with the so-called "detoxification phobia" (Gentile & Milby, 1992) and with the organic mood syndrome or post-methadone syndrome (Kanof et al., 1993; Wermuth & Brummet., 1987). Also, in line with other international studies, the efficacy of the intervention was related to patient-clinic staff agreement, pharmacotherapy support and social care during dose reduction (Cushman, 1981; Gentile & Milby, 1992; Kanof et al., 1993; Stimmel & Rabin, 1974; Tennant & Shannon, 1978; Wermuth & Brummet, 1987). This finding opens up a new insight for our research, under the clinical utility of knowing empirically the factors linked to stress and thus improving the psychological conditions of patients entering methadone withdrawal treatment.

The hypothesis of our study considered that affective states, competences, heroin, cocaine or benzodiazepine use and lifestyle could be related to perceived stress. The results of simple regression analysis confirmed the global nature of this hypothesis. The use of cannabis and alcohol did not reach statistical significance, but heroin, cocaine and benzodiazepine use did. Also the lifestyle acquired during the maintenance treatment had a significant relationship with the stress level of the patients' coping with methadone withdrawal. All these factors could be used to establish, via multivariate statistical procedures, the set of psychological factors with a higher capacity to predict perceived

stress, and the result was the group formed by anxiety, depression, self-control, social support and use of benzodiazepines; the first two indicated a direct relationship with stress and the next two an inverse relationship; benzodiazepine use, also had a direct relationship with stress. Therefore, greater emotional disorder and lower competence level, higher stress level results; psychoactive drugs like benzodiazepines should not be indicated, at least exclusively, whereas psychological procedures ought to be used in order to reduce and control perceived stress level.

Several studies on addiction processes have shown the relationship of stress with anxiety and depression disorders, including post-traumatic stress disorder and increased risk of substance abuse disorder (Leri et al., 2004; Liao et al., 2011; Sinha, 2001). And some studies based on psychological models have related perceived stress to coping skills. According to several authors, drug-cue repeated exposure can induce craving and increase the risk of relapse (Goeders, 2004; Hyman et al., 2007; Hyman et al., 2009; Sinha, 2008; Turner & Lloyd, 2003). Hyman and colleagues (2007) found differences between stress-induced relapse and drug-cue-induced relapse. In the first case, drug craving was associated with high levels of anxiety, fear and sadness, whereas for drug-cue induced craving, this increase of negative emotions did not occur. These authors subsequently observed that opioid-dependent individuals treated with antagonists had higher levels of stress and used less adaptive coping strategies than the control group to which they were compared. Their findings showed that several factors were associated with perceived stress: problem-focused coping, emotion-focused coping, maladaptive avoidance coping and social support; and they established the predictive value of two of them: maladaptive avoidance coping and social support. These results are similar to those of our study.

Relationship with stress has been also investigated in relation to other competences such as self-control. In a review with adolescent population, Sinha (2008) highlighted that acute emotional stress was associated with low control of impulses, inability to inhibit inappropriate behaviors and to delay reinforcement, which involved a risk factor for substance abuse and other maladaptive behaviors in this population. Ladero, Orejudo, and Carrobles (2005), reported that self-efficacy and social support were related to compliance with anti-retroviral treatments in drug-dependent population on MMT.

Finally, our results indicated that benzodiazepine use increased stress perception. Recent studies have reported the risk of using benzodiazepines in patients on MMT, highlighting the high prevalence of abuse risk markers in this population (Carreras, 2007), mentioning the effect of withdrawal on sleep regulation and its relationship with chronic pain, high doses of methadone and psychiatric disorders (Peles, Schreiber, & Adelson, 2005), or considering that benzodiazepine prescription misuse in this population can increase the risk of overdose and relapse in patients discontinuing opioid use (Chen et al., 2011).

The conclusions of this study therefore support considering that psychological factors related to perceived stress can contribute to planning an interdisciplinary intervention in methadone maintenance treatments. This is particularly so in the final stage, but also throughout the therapeutic process if it is intended to promote a change in lifestyle and generate competences that increase the probability of social adjustment and lasting drug abstinence.

This study is not without limitations. First, it shares a common limitation of this kind of studies related to small sample sizes. Sample size was acceptable for the detoxification phase analysis, but was notably reduced during posttreatment. Thus, these results should be taken with caution and should be further examined in the future using larger samples. Another limitation stemmed from the difficulties in measuring competences. While the PIV questionnaire has been used in drug-dependent individuals, it has not been used in previous similar studies and it is therefore necessary to be cautious when comparing findings.

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