Pacini Editore & AU CNS

Regular Article

Heroin Addict Relat Clin Probl 2009; 11(2): 21-30

HEROIN ADDICTION & RELATED CLINICAL PROBLEMS
www.europad.org

Clinical Trial on the Use of Olanzapine in Reducing the Consumption of Cocaine in Methadone Maintenance Programmes

Miguel Landabaso Vázquez [1], Ioseba Iraurgi Castillo [2], Juan Manuel Jiménez-Lerma [3], José Antonio Hormaechea Beldarrain [4], and Miguel Gutiérrez-Fraile [5]

1. Drug-Abuse Treatment Centre in Barakaldo, Bizkaia, Spain
2. Psycho-social Assistance Module in Rekalde, Bilbao, Bizkaia, Spain.
3. Drug-Abuse Treatment Centre in Vitoria-Gasteiz, Alava, Spain.
4. Psychiatry Department - Euskalduna Clinic, Bilbao, Bizkaia, Spain.
5. Psychiatry Department - Cruces Hospital, Bizkaia, Spain.

Summary

The consumption of cocaine among people included in Methadone Maintenance Therapy (MMT) is a widely identified phenomenon, but clinical experience and the literature have highlighted the difficulty of finding an effective pharmacological alternative for cocaine abusers. The aim of this study was to assess the use of olanzapine as a therapy for reducing the use of cocaine in MMT while implementing a more controlled design. A randomized clinical trial has been applied to 60 subjects assigned to three MMT programmes. The independent variable was treatment with olanzapine at three dose levels (0, 5 and 10 mg/day), with three treatment groups being formed; they comprised 20, 21 and 19 subjects, respectively. The outcome variable was the percentage of positive urine tests for cocaine consumption, as estimated by means of urine monitoring using immunoassay, during the first three months after the start of treatment. For the data analysis, MANOVA and the hierarchical regression model were used. The mean proportion of previous cocaine consumption was 25.8% (S.D.= 26.4; range 0-100), with no differences between the treatment groups ($F_{(2,57)} = 0.167$; $p = 0.845$). Hierarchical regression analysis showed a significant model in final step ($F_{(5,54)} = 8.61$; $p \leq 0.001$), with an explained variance of 44.3% ($R^2 = 0.443$). The semi-partial correlation coefficients (r_{s-m}) indicated significant effects on the variables: methadone dose ($r_{s-m} = -0.229$), previous cocaine consumption ($r_{s-m} = 0.345$) and treatment with 5 mg/day ($r_{s-m} = -0.469$) and 10 mg/day ($r_{s-m} = -0.514$) of olanzapine. The mean proportion of positive control results in the untreated subjects was 21%, whereas, in the patients receiving olanzapine therapy, it was 8.8% in those taking a dose of 5 mg/day and 9.5% in those on a dose of 10 mg/day. The prior consumption of cocaine is shown to be a risk predictor for subsequent consumption, whereas an increase in the dose of methadone or treatment with olanzapine both show a protective effect. Specifically, the 10 mg dose of olanzapine, when followed by the 5 mg dose shows the highest degree of explained variance in post-treatment cocaine consumption, after checking the effects induced by the remaining variables.

*Key Words:*Cocaine; Methadone Maintenance Therapy; Olanzapine; Clinical trial

1. Introduction

Nowadays, the most widespread and effective forms of treatment for addiction to opiates [2,28,38,47,48] are replacement therapy or methadone maintenance therapy (MMT); a major complication is that many users of these programmes are consumers of multiple other substances [30,20]. In this respect, the consumption of cocaine in patients receiving MMT is a widely described phenomenon that tends to rise over earlier consumption levels and significantly hinders patients' evolution [6,12,19,21,23,35,41,43].

Among the variables associated with cocaine consumption during MMT, the consumption of cocaine prior to treatment with methadone has been described as the main risk factor [6,19,21,41]; on the other hand, the larger the amount of the methadone dose, and the longer the time the patient has stayed in an MMT programme, the greater the protective effects, even if each of these two parameters has been proposed as a risk factor [8,14,42].

Correspondence: Miguel Landabaso Vázquez. Centro de Tratamiento de Toxicomanias de Barakaldo. C/ Berriotxoa 2. 48903 - Barakaldo-Bizkaia. Spain, EU.
E-mail: miguelangel.landabasovazquez@osakidetza.net

With respect to treatment, both clinical experience and the literature have highlighted the difficulty of finding an effective drug for cocaine abusers [1]. Basic research has presented evidence suggesting the involvement of the dopaminergic and serotoninergic systems, among others, in the action mechanism of cocaine and the use of dopaminergic antagonists to reduce the self-administration of cocaine in animal models [31,36]. In this connection, atypical neuroleptics such as olanzapine, which is able to block dopamine D2 receptors, as well as serotonin receptors 5HT2A and 5HT2C, may be able to reduce the euphoric effects of cocaine and attenuate reinforcement and cocaine craving [29,30,32,37,49]. In this sense, some clinicians have mooted the idea that olanzapine may be able to reduce cocaine use in patients who abuse this substance [4,22,24,25]. In addition, olanzapine may be superior to traditional neuroleptics in treating cocaine dependence, due to its less severe side-effect profile [5,26].

There is evidence both for [9,18,27,40] and against [22] the usefulness of atypical neuroleptics in reducing cocaine consumption in humans. Previous studies by our group using less well-controlled designs [24,25] offered promising results on the use of olanzapine in patients addicted to opiates who were receiving treatment with methadone after there had been an increase in cocaine abuse while they stayed in the MMT programme. In this paper our aim is to offer results based on a better controlled design that allows olanzapine therapy to be assessed for its capacity to reduce cocaine abuse in patients without psychotic symptoms who are still on an MMT programme.

2. Materials and methods

2.1. Subjects

The study sample comprised 60 people with DSM-IV criteria for opiate dependency and receiving MMT, where there had been an increase in cocaine consumption after

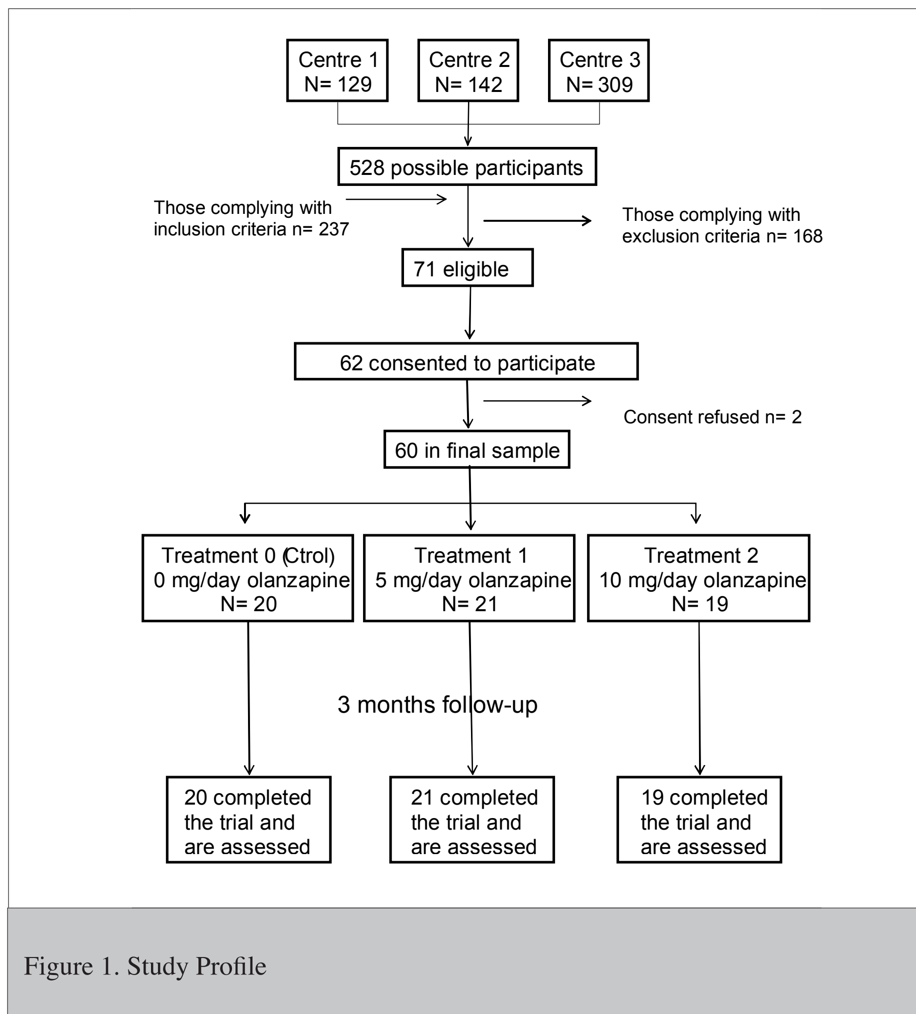

Figure 1. Study Profile

stabilization of the methadone dose.

Of the 60 participants, 48 were male and 12 were female (80% versus 20%), ranging between 23 and 46 years of age (mean = 35.5; SD = 4.8), and they were mainly single (58.4%) or separated (16.7%). The mean time on the MMT programme was 6.3 months (SD = 2.4), with the longest participation stretching to 11.7 months. The doses of methadone dispensed varied between a minimum of 10 mg/day and a maximum of 150 mg/day (Mean = 66.4; SD = 28.5).

The research protocol was approved by the health services' ethics committee. All the subjects taking part received information about the characteristics of the trial and their informed consent was obtained prior to participation.

2.2.- Procedure

The trial has involved the participation of 3 Drug Abuse Treatment Centres (CTT in their Spanish acronym) located in the Basque Country (Spain). From the total number of patients receiving treatment in the MMT programmes operative at these three CTTs (n = 528), after applying the inclusion and exclusion criteria, an eligible sample of 71 subjects was obtained, with 62 of them (87.3%) giving their consent to participation. CTT-1 contributed 15 subjects, CTT-2 21 and CTT-3 24. Lastly, one subject from CTT-1 and another one from CTT-2 withdrew before starting the study, so the final sample comprised 60 participants (Figure 1).

One of the inclusion criteria for admission to the trial was that the participants had to show an increase in their consumption of cocaine after the start of treatment with methadone compared with that recorded previously. During the three months prior to the start of the study, there was a selection of those subjects who had delivered more than 15% of cocaine-positive samples (237/528) during the routine substance detection tests.

The exclusion criteria applied were:

1) the presence of psychotic symptoms, dementia disorders, major or bipolar depression;
2) alcohol consumption in excess of 20 standard units per week for women and 30 standard units a week for men;
3) pregnancy in women; and 4) known hypersensitivity to olanzapine.

After selection, participants were randomly assigned, in a proportion of 1:1:1, to three treatment modes with olanzapine: '0', '5' and '10' milligrams a day. For the randomization process, each participant was given a consecutive number, and the distribution of patients among the treatment groups was performed using Epidata software [33]. The outcome of this randomization was as follows: 0 mg (n=20), 5 mg group (n=21) and 10 mg group (n=19). No masking techniques were used for the administration of the therapy i.e. neither the patients nor the physicians were blinded, but blinding was used for the data analysis.

A study period of 3 months was set. Every day, each participant was given the appropriate prescribed dose of methadone, and the treatment with olanzapine assigned to them; both doses were taken in situ, except in the case of doses intended for the weekends, which were delivered on Friday for self-administration on the scheduled days. Furthermore, all the subjects received a weekly counselling session where the effects of the therapy and the prevention of relapses were discussed. These sessions were homogeneously structured and administered by the clinicians at each of the participating CTTs. On the other hand, all the participants were being medicated with benzodiazepines in a variety of pharmacological formats and doses that had been prescribed prior to the start of the trial. This variable was not systematically controlled in view of the diversity of sub-groups that might arise from this classification, and the randomized assignation was assumed to have distributed the resulting effects homogeneously.

The main outcome parameter assessed in this trial was the consumption of cocaine during the last 2 months of the study period after therapy with olanzapine had been initiated. Estimations were made based on urine samples collected for the determination of cocaine metabolites. As part of the protocol, each of the participating CTTs collected urine samples weekly and selected the collection day at random. The analyses were performed using homogeneous enzyme immunoassay techniques (EMIT) in a COBAS-MIRA analyzer, using SYVA reagents, calibrators and control samples, and an external control of DOA at two negative and positive levels, with the results stored in a computerized database. For each subject the number of tests performed was noted, along with the number of positive results in each case, so as to give an estimate of the ratio between these 2 variables (Nº positives / Nº tests); this procedure yielded an index expressing the Proportion of Consumption (PC) of this substance. For example, a subject for whom 20 determinations of cocaine have been made, with none of them positive, will have a PC of 0 (0/20); this expresses the subject's situation in terms of his/her degree of abstinence from cocaine; if, on the other hand, there had been 8 positive tests recorded, the PC would be 0.4 (8/20), in other words the subject has presented consumption of cocaine on 40% of the occasions analyzed. PC values vary between 0 and 1, with the level of substance use increasing as the value comes closer to 1.

2.3.- Statistical analyses

All of the analyses were performed using the SPSS software. Tally and proportion procedures were used, together with central trend and dispersion statistics for the description of the sample.

In order to verify whether the random assignation had produced a compensation effect, an analysis was carried

out on the contrast between the differences in the pre-treatment characteristics of the sample, depending on the assignation groups they belonged to. To do so, the Chi square test was used for category data and a variance analysis for continuous data.

The effect of treatment with olanzapine on the reduction of cocaine consumption was assessed through two procedures. First of all, a multiple analysis of variance model (MANOVA) was used to compare the inter-group, intra-subject and interaction effects. In order to determine where the differences between the treatment groups occurred, the post hoc contrasts based on the Bonferroni test were used; for the post hoc comparisons found in the change in each group between the baseline and post-treatment values, the t-test for paired data was used.

Secondly, a hierarchical multiple regression model was used to determine the direct and indirect effects of each level of treatment with olanzapine and the possible co-variables (the percentage of cocaine consumption in the pre-treatment period, the duration of participation in the methadone programme and the methadone dose dispensed) on cocaine consumption after treatment. Model 1 includes the treatment with olanzapine variable in a dummy format, taking the no-treatment group as its term of reference (0 mg of olanzapine). Models 2, 3 and 4 include, in order, the aforesaid co-variables in order to check the effect of the main variable and assess the contribution of each of these co-variables. The results of all regressions were presented through semi-partial correlation coefficients for each predictor variable, along with overall F values and adjusted R^2. Semi-partial correlation coefficients were chosen over other possible coefficients (e.g. partial correlation, beta weights) because they represent the proportion of variance in the dependent values uniquely associated with a particular predictor variable [11].

3. Results

There were no withdrawals from treatment nor was it necessary to intervene or alter the therapy in any case. Nor were any significant side-effects noticed, except for weight gain in 16 of the participants (26.6%).

The randomized assignation of the subjects to the treatment groups allowed a homogeneous distribution of the pre-treatment variables to be obtained. None of the variables assessed has shown statistically significant differences (Age: $F_{(2,57)}$= 0.088; p= 0.916 / Gender: $\chi^2_{(2)}$= 1.91; p=0.384 / mean time with MMT programme: $F_{(2,57)}$= 1.780; p= 0.178 / Methadone dose: $F_{(2,57)}$= 0.180; p= 0.836; Proportion of positive cocaine consumption tests during the three months prior to the start of treatment: $F_{(2,57)}$= 0.167; p= 0.845).

Figure 2 represents the degree of cocaine consumption before and after treatment through the prevalence of positive results in the cocaine consumption tests, and

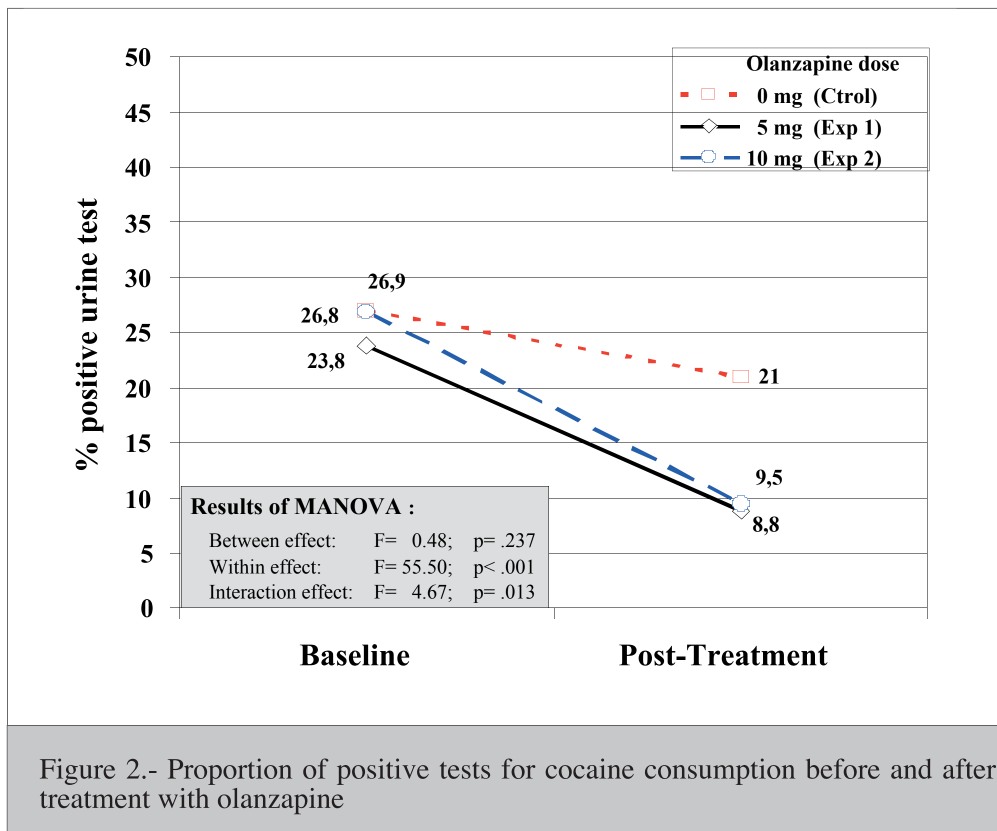

Figure 2.- Proportion of positive tests for cocaine consumption before and after treatment with olanzapine

the F values in the MANOVA. Both the intra-subject effect and interaction have been shown to have statistical significance. A post hoc analysis concluded that the differences between the groups after treatment [$F_{(2,57)} = 6.17$; $p = 0.004$] were between those treated with olanzapine (5 or 10 mg) and those who were not treated (0 mg). Furthermore, a fall in the consumption of cocaine before and after treatment occurs in the groups treated with 5 mg [$t_{(18)}= 5.04$; $p< 0.001$] and 10 mg of olanzapine [$t_{(20)}= 6.03$; $p< 0.001$], but not in the untreated group [$t_{(19)}= 1.86$; $p= 0.078$].

Table 1 presents the semi-partial correlation coefficients of the treatment variable and other co-variables of interest, as well as the R^2 and the increase in R^2 produced at each step in the hierarchical regression used. The first step included the main variable under study, and this alone was enough to account for 25.3% of the variance. The semi-partial correlation coefficients for the 5 mg and 10 mg doses are negative, above the value of 0.40 and very closely bunched. Step 2 includes the variable 'prevalence of cocaine positive tests in the three months prior to the start of the study' and there was an increase of 0.137 in R^2, with a semi-partial correlation of 0.37. The incorporation of this variable promotes a change in the semi-partial correlation values of the 5 mg (-0.47) and 10 mg (-0.52) doses. Step 3 incorporates the variable 'months of participation in the methadone programme' and fails to produce any significant changes. Step 4 incorporates the 'methadone dose' and promotes an increase of 0.05 points in R^2, which in this last model reaches a value of 0.44. The semi-partial correlation coefficient associated with the methadone dose is -0.23; it does not substantially alter the magnitude of the coefficients attained by the other variables included in the model.

4. Discussion

The results obtained provide evidence in favour of acceptance of the hypothesis that the use of olanzapine may be useful in reducing cocaine consumption, at least in subjects on MMT who continue to use this substance.

The bivariate analysis of the study factor has shown statistically significant differences in favour of the groups treated with olanzapine over the control group, although it has not allowed differences to be established in terms of the olanzapine dose used (5 mg versus 10 mg). Subjects treated with olanzapine show a much lower mean proportion of cocaine use after treatment than those not treated (a reduction of 16.15% versus 5.9%, respectively). Olanzapine is a powerful antagonist of 5-HT2a receptors (saturating them with a dose of 5 mg [15]) located in the glutamatergic pyramidal neurons of most of the cortical regions [30]; agents with significant affinity for 5-HT2a receptors antagonize hyperactivity, reversing the symptoms produced by the non-competitive antagonists of the NMDA receptor [30,49]. It is likely that the combined action of olanzapine on the dopaminergic, serotoninergic and glutamatergic systems [7,16], and its probable ability to reduce depression [44,45], may help to reduce cocaine consumption.

It must be noted that other studies [13,17,34] with serotoninergic drugs (SSRIs) were inconclusive on the issue of the reduced consumption of cocaine, although they did report a decline in depressive symptoms, probably through its sole serotoninergic action. Furthermore, those studies [4,5,9,18,24,25,26,27,39,40,46] showing the efficacy of atypical neuroleptics had the aim of treating patients with dual pathology or patients taking part in an MMT programme, as in this paper; however, the only study [22] that failed to show efficacy had the aim of treating patients with cocaine dependency. It may be that the effects of the atypical antipsychotics on symptoms of schizophrenia, particularly the negative symptoms, will prove to make these medications useful to cocaine-dependent patients with schizophrenia. At the present time, it is probably not appropriate to seek a global or

Table 1. Hierarchical linear regression on the percentage of cocaine consumption after treatment (semi-partial correlation coefficients)

	Step 1	Step 2	Step 3	Step 4
Olanzapine Dosage: 5 mg/day (Dummy variables) 10 mg/day	-0.440** -0.430**	-0.469** -0.518**	-0.465** -0.516**	-0.469** -0.514**
Previous Cocaine Consumption (% positive controls)		0.370**	0.343**	0.345**
Time with MMT			-0.014	0.050
Methadone Dosage in mg/day				-0.229*
F	9.674	11.991	8.843	8.617
R^2	0.253	0.391	0.392	0.443
ΔR^2		0.137	0.001	0.052

* p<0.05; ** p<0.001; all regressions significant (p<0.001)

universal treatment for all consumers of cocaine, but, rather, to undertake a selective search for patients with specific characteristics, where these or other drugs might be effective in such dependencies.

Other authors in our setting have described an increase in the plasma levels of methadone in patients participating in MMT programmes treated with SSRIs [3] and/or OLZ [4], which may allow reductions in daily doses of methadone – reductions that may have a subjective positive effect on patients in MMT programmes as they relate dose reduction to improvement.

It is noteworthy that 100% of the patients included in the study completed it, indicating a scant incidence of side-effects deriving from olanzapine administration, unlike what happens with typical neuroleptics in addiction clinics where cases of early withdrawal due to side-effects were a majority. Attention should be drawn to the scant incidence of side-effects, except for weight gain, but in this kind of patient, with many years of cocaine use, mostly infected with HIV and with considerable organic deterioration, weight gain might almost be considered to be a beneficial effect.

The multivariate analysis, on the other hand, allows certain important observations to be drawn. First of all, the findings obtained in the bivariate analysis are ratified, with the first step in the hierarchical regression presenting a very similar effect between the doses of olanzapine used (semi-partial correlations of -0.44 and -0.43 for the 5 mg and 10 mg doses, respectively); in addition, it is the variable that shows the greatest protective effect on the consumption of cocaine after treatment (25% of the variance explained).

The risk factor with the second greatest effect on the outcome variable is the prior consumption of cocaine, which turns out to be a factor predicting future consumption or continuation of consumption (r_{sp}= 0.37). This risk effect was already well-known [6,14,19,21], but the inclusion of this variable in the model has brought about an effect on the main variable: a modification in the magnitude of the semi-partial correlations of the doses of olanzapine. When the effect of prior consumption of cocaine is controlled, an increase in the protective effect of olanzapine is observed; this effect is greater in the case of the 10 mg dose (r_{sp}= -0.43 to r_{sp}= -0.52; Δ= 0.09) than for 5 mg (r_{sp}= -0.44 to r_{sp}= -0.47; Δ= 0.03).

A third variable that, like the first two, shows a significant effect on the reduction of cocaine consumption among users receiving MMT is the dose of methadone dispensed. The effect is moderately low (an increase of 5.2% in the variance explained by the regression model and an r_{sp}= -0.23), yet it indicates that a greater dose of methadone is likely to be associated with a lower consumption of cocaine during MMT. Furthermore, this variable does not interact with the other variables included in the model, because the magnitude and the sense of the semi-partial correlations of those other variables are not altered by it.

On the other hand, the longer or shorter participation in MMT programmes, in other words the duration of the period spent in methadone treatment, does not influence cocaine consumption during the programme.

Although the results obtained provide evidence of an appropriate degree of effectiveness in the use of olanzapine for the reduction of cocaine use among patients receiving MMT, we feel that further studies are now required to corroborate these findings. The use of randomization for the assignation of subjects and the composition of the treatment groups have, we feel, neutralized the impact of variables not assessed in our study. No doubt a wider-ranging assessment, capable of taking into account other predictive variables analysed in other studies [21,22], would allow us a greater degree of breakdown regarding the factors involved in cocaine consumption during MMT. As clinicians, we have given priority to flexibility and the naturalness of treatment in order to avoid instrumentation effects through the assessment of a few relevant variables measured indirectly; as proponents of scientific knowledge, we are aware of the limitations implied by proceeding in this way. For this reason, further studies should be undertaken to overcome these limitations; this would allow an answer to be given, while the hypotheses put forward by us to account for our results could then be accurately assessed.

5. Conclusions

The previous level of cocaine consumption proves to be a risk predictor for subsequent consumption, whereas an increase in methadone dose or in the treatment with olanzapine has a protective effect.

Treatment with olanzapine, whether at a dose of 10 mg/24 hr or at a dose of 5 mg/24 hr, is the factor which has the greatest effect on the reduction of cocaine consumption in patients currently in methadone maintenance programmes who are addicted to opiates and who continue to consume cocaine during treatment.

Rerefences

1. AMERICAN PSYCHIATRIC ASSOCIATION. (1995). Cocaine related disorders: Treatment principles and alternatives. Am J Psychiatry 152 (suppl): 36-39.
2. BALL J.C., ROSS A. (1991). The effectiveness of methadone maintenance treatment: patients programs, services and outcomes. Springer-Verlag, New York.
3. BAÑO M.D., AGUJETAS M., LÓPEZ M.L., TENA T., RODRÍGUEZ A., LORA-TAMAYO C., GUILLÉN J.L. (1999). Eficacia de la fluoxetina en el tratamiento de la adicción a cocaína en pacientes en mantenimiento con metadona y su interacción en los niveles plasmáticos / Fluoxetine (FX) efficacy in the treatment of cocaine dependence in methadone

maintenance patients. Interaction with plasma levels. Actas Esp Psiquiatr 27: 321-324.

4. BAÑO M.D., MICO J.A., AGUJETAS M., LÓPEZ M.L., GUILLEN J.L. (2001). Eficacia de antipsicótico olanzapina en el tratamiento del abuso de cocaína en pacientes en mantenimiento con metadona. Interacción en los niveles plasmáticos / Olanzapine efficacy in the treatment of cocaine abuse in methadone maintenance patients. Interaction with plasma levels. Actas Esp Psiquiatr 29: 215-220.
5. BERK M., BROOKS S., TRANDAFIR A. (1999). A comparison of olanzapine with haloperidol in cannabis-induced psychotic disorder: a double-blind, randomized controlled trial. Int Clin Psychopharmacol 14 (3): 177-180.
6. BORG L., BROE D.M., HO A., KREEK M.J. (1999). Cocaine abuse sharply reduced in an effective methadone maintenance program. J Addict Dis 18 (4): 63-75.
7. CALLADO L.F., MEANA J.J. (2001). Neurolépticos atípicos y consumo de sustancias: Bases farmacológicas / Atypical neuroleptics and susbtance abuse: Pharmacological basis. Trastornos Adictivos 3: 7-18.
8. CAPLEHORN J.R., BELL J., KLEINBAUM D.G., GEBSKI V.J. (1993). Methadone dose and heroin use during maintenance treatment. Addiction 88 (1): 119-124.
9. CASAS M., GUTIÉRREZ M., GIBERT J., BOBES J., RONCERO C., OCTAVIO I. (2001). Risperidona en el tratamiento de pacientes psicóticos con abuso y dependencia de opiáceos / Risperidone in the treatment of psychotic patients with opiate abuse and dependence. Actas Esp Psiquiatr 29: 380-385.
10. CHATHAM L.R., ROWAN-SZAL G.A., JOE G.W., BROWN B.S., SIMPSON D.D. (1995). Heavy drinking in a population of methadone maintenance clients. J Stud Alcohol 56 (4): 417-422.
11. COHEN J., COHEN P. (1983). Aplied Multiple Regression / Correlation Analysis for the Behavioral Sciences. Hillsdale, NJ; Erlbaum.
12. CONDELLI W.S., FAIRBANK J.A., DENNIS M.L., RACHAL J.V. (1991). Cocaine use by clients in methadone programs: significance, scope and behavioural interventions. J Subst Abuse Treat 8 (4): 203-212.
13. COVI L., HESS J.M., KREITER N.A., HUERTZEN C.A. (1995). Effects of combined fluoxetine and counseling in the outpatients treatment of cocaine abusers. Am J Drug Alcohol Abuse 21 (3): 327-344.
14. DUNTEMANT G.H., CONDELLI W.S., FAIRBANK J.A. (1992). Predicting cocaine use among methadone patients: analysis of findings from a national study. Hosp Community Psychiatry 43 (12): 1245-1246.
15. FULTON B., GOA K.L. (1997). Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. Drugs 53 (2): 281-298.
16. GLEASON S.D., SHANNON H.E. (1997). Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine and serotonin receptor subtype selective antagonists in mice. Psychopharmacology (Berl.) 129 (1): 79-84.
17. GRABOWSKI J., RHOADES H., ELK R., SCHMITZ J., DAWIS C.H., CRESON D., KIRBY K. (1995). Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opiate and cocaine dependence: two placebo-controlled double-blind trials. J Clin Psychopharmacol 15 (3): 163-174.
18. GRABOWSKY J., RHOADES H., SILVERMAN P., SCHMITZ J.M., STOTTS A., CRESON D., BAILEY R. (2000). Risperidone for the treatment of cocaine dependence: Randomized, double-blind trial. J Clin Psychopharmacol 20 (3): 305-310.
19. HARTEL D.M., SCHOENBAUM E.E., SELWYN P.A., KLINE J., DAVENNY K., KLEIN R.S., FRIEDLAND G.H. (1995). Heroin use during methadone maintenance treatment: The importance of methadone dose and cocaine use. Am J Public Health 85 (1): 83-88.
20. IRAURGI I., AIZPURU A., PINILLA E., MARCOS J.J., UNDA J., ORMAETXEA B., CASAS A., TOMÁS M.A., TORRE M.A., OMAGOXEASKOA I. (2002). Consumo de substances durante un programa de mantenimiento con Methadone / Drug use during Methadone Maintenance Program. Psiquiatría Biológica 9: 109-115.
21. IRAURGI I., CASAS A. (1999). Factores Asociados al uso de opiáceos en un Programa de Mantenimiento con Metadona / Associated factors to opiate use during a Methadone Maintenance Programme. Rev Esp Drogodep 24: 389-400.
22. KAMPMAN K.M, PETTINATI H., LYNCH K.G, SPARKMAN T.H, O'BRIEN CH.P. (2003). A pilot trial of Olanzapine for the treatment of cocaine dependence. Drug Alcohol Depend 70 (3): 265-273.
23. KIDORF M., STITZER M.L. (1993). Descriptive analysis of cocaine use of methadone patients. Drug Alcohol Depend 32 (3): 267-275.
24. LANDABASO M., IRAURGI I., JIMÉNEZ-LERMA J.M., HORMAECHEA J.A., SANZ J., CALLE R., LARRAZABAL A., AIZPURU A., GUTIÉRREZ M. (2003). Olanzapina y consumo de cocaína en programas de mantenimiento con metadona: nuevos resultados / Olanzapine and cocaine consumption in Methadone Maintenance Programs: New results. Psiquiatría Biológica 10(5): 160-164.
25. LANDABASO M., IRAURGI I., JIMÉNEZ-LERMA J.M., SANZ J., CALLE R., LARRAZABAL A., AIZPURU A., GUTIÉRREZ M. (2001). Olanzapina y consumo de cocaína en programa de mantenimiento

con metadona / Olanzapine and cocaine consumption in Methadone Maintenance Programs. Psiquiatría Biológica 8: 171-174.
26. LEUCHT S., PITSCHEL-WALTZ G., ABRAHAM D., KISSLING W. (1999). Efficacy and extrapyramidal side effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophr Res 35 (1): 51-68.
27. LITTREL K.H., PETTY R.G., HILLIGOSS N.M., PEABODY C.D., JOHNSON C.G. (2001). Olanzapine treatment for patients with schizophrenia and substance abuse. J Subt Abuse Treat 21 (4): 217-221.
28. MARSCH L.A. (1998). The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. Addiction 93 (4): 515-532.
29. MCCREARY A.C., CUNNINGHAM K.A. (1999). Effects of the 5HT2C/2B antagonist SB 206553 on hyperactivity induced by cocaine. Neuropsychopharmacology 20 (6): 556-564.
30. MCMAHON L., CUNNINGHAM K. (2001). Role of 5-HT2A and 5-HT2B/2C receptors in the behavioral interactions between serotonin and catecholamine re-uptake inhibitors. Neuropsychopharmacology 24 (3): 319-329.
31. MEIL W.M., SCHECHTER M.D. (1997). Olanzapine attenuates the reinforcing effects of cocaine. Eur J Pharmacol 340 (1): 17-26.
32. O'NEILL M., HERON-MAXWELL C., SHAW G. (1999). 5HT receptor antagonism reduces hyperactivity induced by amphetamine cocaine and MK801 but not D1 agonist C-APB. Pharmacol Biochem Behav 63 (2): 237-243.
33. ORGANIZACIÓN PANAMERICANA DE LA SALUD / PAN-AMERICAN HEALTH ORGANIZATION. (1997). EPIDATA. Análisis epidemiológico de datos tabulados / Epidemiologic analysis of tabulated data. Version 2 for Windows. Xunta de Galicia.
34. PETRAKIS I., CARROLL K., GORDON L., CUSHING G., ROUSANVILLE B. (1994). Fluoxetine treatment for dually diagnosed methadone maintained opioid addicts: a pilot study. J Addict Dis 13 (3): 25-32.
35. PRESTON K.L., SILVERMAN K., SCHUSTER C.R., CONE E.J. (1997). Assessment of cocaine use with quantitative urinalysis and estimation of new uses. Addiction 92 (6): 717-727.
36. RASMUSSEN T., SAUERBERG P., NIELSEN E., SWEDBERG M., THOMSEN C., SHEARDOWN M., JEPPESEN L., CALLIGARO D., DELAPP N., WHITESITT C., WARD J., SHANNON H., BYMASTER F., FINK-JENSEN A. (2000). Muscarinic receptor agonists decrease cocaine self-administration rates in drug-naive mice. Eur J Pharmacol 402 (3): 241-246.
37. ROCHA B.A., FUGAMALLI F., GAINETDINOV R.R., JONES S.R., ATOR A., MILLER G.W., CARON M.G. (1998). Cocaine self-administration in dopamine-transporter knock-out mice. Nature Neurosci 1:132-137.
38. SÁNCHEZ-PARDO L. (2000). Evaluación de la efectividad de los programas de sustitutivos opiáceos / Evaluation of the opiate subtitution programs effectiveness. Trastornos Adictivos 1(2): 56-72.
39. SAYERS S.L., CAMPBELL E.C., KONDRICH J., MANN S.C., CORNISH J., O'BRIEN C., CAROFF S.N. (2005). Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. J Nerv Ment Dis 193 (6): 379-386.
40. SMELSON D.A., LOSONCZY M.F., DAVIS C.W., KAUNE M., WILLIAMS J., ZIEDONIS D. (2002). Risperidone deceases craving and relapses in individuals with schizophrenia and cocaine dependence. Can J Psychiatry 47 (7): 671-675.
41. STINE S., SATEL S., KOSTEN T. (1993). Cocaine precipitates patient-identified opiate withdrawal. Am J Addiction 2: 255-258. 12
42. STRAIN E.C., STITZER M.L., LIEBSON I.A., BIGELOW G.E. (1993). Dose-response effects of methadone in the treatment of opioid dependence. Ann Inter Med 119 (1): 23-27.
43. STRUG D.L., HUNT D.E., GOLDSMITH D.S., LIPTON D.S., SPUNT B. (1985). Patterns of cocaine use among methadone clients. Int J Addict 20 (8): 1163-1175.
44. TOLLEFSON G.D., ANDERSEN S.W. (1999). Should we consider mood disturbance in schizophrenia as an important determinant of quality of life. J Clin Psychtriatr 60 Suppl 5: 23-29.
45. TRAN P.V., HAMILTON S.H., KUNTZ A.J., POTVIN J.H., ANDERSEN S.W., BEASLEY C., TOLLEFSON G.D. (1997). Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 17 (5): 407-418.
46. TSUANG J., MARDER S.R., HAN A., HSIEH W. (2002). Olanzapine treatment for patients with schizophrenia and cocaine abuse. J Clin Psychiatry 63 (12): 1180-1.
47. VAN BEUSEKOM I., IGUCHI M. (2001). A review of recent advances in knowledge about methadone maintenance treatment. RAND Corporation. http://www.rand.org/publications/ MR/MR1096
48. WARD J., HALL W., MATTICK R.P. (1999). Role of maintenance treatment in opioid dependence. Lancet 353 (9148): 221-226.
49. WILLINS D.L., DEUTCH A.Y., ROTH B.L. (1997). Serotonin 5-HT2A receptors are expressed on pyramidal cells and interneurons in the rat cortex.

Synapse 27 (1): 79-82.

Role of funding source

This study was supported by internal funds

Contributors

The authors contributed equally to this work.

Conflict of Interest

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

Received October 23, 2008 - Accepted May 1, 2009