Aripiprazole and Ropinirole Treatment for Cocaine Dependence: Evidence from a Pilot Study

M. Meini, M. Moncini, D. Cecconi, V. Cellesi, L. Biasci, G. Simoni [§], M. Ameglio **, M. Pellegrini **, R.N. Forgione [#] and P. Rucci *

*Drug Addiction Department, Local Health Trust 5, Via Fleming 1, 56025 Pontedera, Pisa, Italy, [§] Drug Addiction Department, Local Health Trust 1, Viale XX Settembre, 54033 Carrara (MS), Italy, [**] Drug Addiction Department, Local Health Trust 7, Siena Via Pian d'Ovile, 11 - 53100 Siena, Italy, [#]Department of Neuroscience, University of Siena School of Medicine, Viale Bracci 1, Siena 53100, Italy, *Department of Medicine and Public Health, University of Bologna, Via San Giacomo 12, 40126 Bologna, Italy*

Abstract: ***Background***: Currently, there is no specific pharmacological therapy with established efficacy for the treatment of cocaine dependence. The aim of this study was to determine the safety, tolerability and the effects of aripiprazole and ropinirole in patients with cocaine dependence.

Methods: This randomized clinical trial of 12-week duration was carried out on 28 consecutive patients with cocaine dependence presenting for treatment. The diagnostic assessment was performed using ICD-9-CM criteria and Mini International Neuropsychiatric Interview. The Clinical Global Impression Scale, a Visual Analogue Scale to assess craving and a self-report questionnaire on the use of cocaine were administered at baseline and then weekly throughout the study. Urinalyses were carried out three times per weeks to search for benzoylecgonine.

Results: Of the 28 study participants, 14 completed the protocol. Treatment discontinuation was unrelated with side effects. One patient required a dosage reduction of ropinirole because of sleepiness and one patient assigned to aripiprazole who reported moderate akathysia had the dosage reduced to 5 mg/day. Routine blood works did not show significant changes from baseline and the overall proportion of positive urinalyses for benzoylecgnonine did not differ significantly between treatments. Using linear mixed-effect models a significant decrease in craving was found in the overall sample ($p<0.001$). The mean number of cocaine administrations exhibited a faster decrease with aripiprazole compared with ropinirole ($p=0.009$).

Conclusions: Our pilot study indicates that cocaine craving decreases with both aripiprazole and ropinirole treatment but aripiprazole is more efficacious in reducing cocaine use.

Keywords: Cocaine dependence, aripiprazole, ropinirole, craving.

INTRODUCTION

Cocaine use is an important public health problem worldwide with major medical, psychological and social and legal implications, including the spread of infectious diseases, crime, violence and neonatal drug exposure. The European Monitoring Center for Drugs and Drug Addiction [1] reported that some 13 million European adults (15–64 years) have tried cocaine in their lifetime. Of these, 7.5 million are young adults (15–34 years), 3 million of whom have used it in the last year. In highest-prevalence countries (Denmark, Spain, Ireland, Italy and the UK), recent surveys show that use in the last year among young adults ranged from 3.1 % to 5.5 %. In most reporting countries, recent data point to a stable or rising trend in last-year use in the 15–34 age group. In Italy, cocaine is the second substance of abuse after cannabis and it is the primary or secondary substance of abuse in about 45% of patients being treated by the Drug Addiction Services [2]. This calls for an urgent need for effective treatments for this condition.

Currently, there is no specific pharmacological therapy with established efficacy for the treatment of cocaine dependence. Therefore information on treatment effects, retention in treatment and safety is warranted for planning clinical trials.

A review on pharmacological treatments of cocaine dependence including antidepressants, carbamazepine, dopamine agonists and other drugs used in the treatment of cocaine dependence [3] did not provide any evidence from randomized clinical trials supporting the clinical use of carbamazepine, antidepressants, dopamine agonists, disulfiram, mazindol, phenytoin, nimodipine, lithium and NeuRecover-SA [4]. A subsequent more recent review by Karila and collegues [5] indicated that pharmacological agents such as GABA agents (topiramate, tiagabine, baclofen and vigabatrin) and agonist replacement agents (modafinil, disulfiram, methylphenidate) seem to be promising in treatment of cocaine dependence, but evidences are still inconclusive [6-10].

Recent advances in neurobiology identified various neuronal mechanisms implicated in cocaine addiction [11-12]. The reported efficacy of dopamine agonists in modulating cocaine and amphetamine self-administration in experimental animals indicates a strong relationship between dopamine receptors and cocaine [13-17]. D_1, D_2 and D_3 receptors seem to be implicated in the mechanism: subchronic cocaine administration seems to straighten the effect of D_2 agonists on sexual behaviour and stretching-yawning of male rats [18]; D3 preferring agonists seem to be able to substitute over 80% for cocaine and 62% for amphetamine; D_1 agonists moderately substitute for cocaine but not for amphetamine. On the contrary D_1 antagonists and D_2 blockers significantly attenuate the effects of psychostimulants [19-21].

Ropinirole is a dopamine agonist active on D_2, D_3 and D_4 receptors, whose efficacy and safety in the treatment of Parkinson disease has been widely demonstrated [22-24]. Due to its effects on affective symptoms in neurologic patients, ropinirole has been used in the treatment of patients with major depression and proved to be efficacious in alleviating depressive symptoms [25-26]. To date, only a pilot open-label trial has been published supporting the efficacy and safety of ropinirole in the treatment of cocaine dependence [27].

The atypical antipsychotic aripiprazole has been the focus of preclinical and clinical evaluations as a potential pharmacotherapy for stimulant use disorders [28-31]. Dopamine D_2-like partial agonists have received some attention as pharmacological treatments of

*Address correspondence to this author at the Department of Medicine and Public Health, University of Bologna, Via San Giacomo 12, 40100 Bologna, Italy; Tel: 051-2094837; Fax 051-2094839; E-mail paola.rucci2@unibo.it

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psychostimulant addiction [4, 21, 32]. Aripiprazole is an atypical antipsychotic drug characterized by partial agonist activity at D_2 and D_3 receptors and a low side-effect profile [16, 33-34].

Feltenstein and collegues [35] provided evidence that aripiprazole can block cocaine seeking in experimental animals without interfering with other behaviours.

Similar results were reported in human healthy volunteers who were not stimulant abusers [36]. Two studies [28, 37] showed that aripiprazole is effective in reducing the discriminative stimulus, the cardiovascular effects and some subjective symptoms typical of amphetamine use.

Moreover, two studies carried out in patients with psychiatric disorders and comorbid cocaine use reported a significant reduction in craving for cocaine during treatment with aripriprazole [38,39]. It is now well established that cocaine and other psychostimulants share a number of pharmacodynamic properties, which leads to the hypothesis that patients using these substances have a similar response to pharmachological treatment.

Evidence from the literature [5, 21] suggests that aripiprazole is an effective treatment strategy for cocaine dependence. In fact, aripiprazole might modulate the dopaminegic firing in the brain caused by cocaine. Moreover, it might reduce the anxiety and dysphoric symptoms during acute intoxication via a modulation of the dopamine release in the mesocortical areas and the serotonin release in the lymbic and cortical areas.

Lastly, in the presence of dopaminergic depletion, aripiprazole might reduce craving and depressive symptoms typical of cocaine withdrawal by virtue of its unique mechanism of action as a partial agonist at dopamine D_2 dopamine receptors and as a dopamine system stabilizer.

Given the limited evidence on the benefits of pharmacological treatments for cocaine dependence, we carried out a phase-II study in subjects seeking treatment for this condition at 7 Drug Addiction Services.

The aim of this study was to determine the safety, tolerability and the effects of aripiprazole and ropinirole in patients with cocaine dependence.

METHODS

This randomized clinical trial was carried out at 7 Drug Addiction Services of Tuscany, Italy, between May 2008 and June 2009 [40].

Inclusion criteria were cocaine dependence, diagnosed using the ICD-9-CM criteria and confirmed by at least 3 positive toxicological tests performed in the 30 days preceding the enrolment. Patients with lifetime psychiatric disorders in full remission, abuse of substances other than cocaine, nicotine abuse/dependence and heroin dependence in treatments with methadone were also included in the study.

Exclusion criteria were: cocaine abuse or dependence in remission, current axis-I psychiatric disorders, organic mental disorders, chronic medical illnesses, hyperglycaemia, suicide attempts or suicidal risk, pregnancy or breast feeding, ongoing psychotropic drug treatments or psychotherapy, being in jail or in a therapeutic community, intolerance to lactose, malabsorption, malignant neuroleptic syndrome, epilepsy.

A list of potentially eligible subjects was generated through a query to the Tuscany Region Information System (SIRT) database, where information on visits and treatment plans of patients with drug abuse or dependence being treated at the Drug Addiction Services of Tuscany has been recorded since 2000.

Patients in the list and new patients presenting for treatment were assessed with the MINI Neuropsychiatric Interview to confirm the presence/absence of eligibility criteria. Patients meeting both the diagnostic and toxicological criteria were asked to participate in the study. Those who accepted to participate were randomly assigned to aripriprazole or ropinirole treatment for 12 weeks.

The randomization list was generated by a statistician using an ad-hoc procedure in SPSS and kept by an administrative staff of the coordinating centre not involved in patient recruitment. Randomization was concealed until inclusion criteria were determined and then communicated to the participating centers.

Aripiprazole was administered once daily at the dosage of 5 mg/day in the first week, that at 10 mg/day from the 2^{nd} to the 12^{th} week of treatment. The dosage could be reduced to 5 mg/day in case of tolerable side effects. If patients could not tolerate the dosage of 5 mg/day, they were terminated from the study.

Ropinirole was administered at the dosage of 0.75 mg/day (0.25 mg three times per day) during the first week and then titrated to 1.5 mg/day (0,50 mg three times per day) from the 2^{nd} to the 12^{th} week. The dosage could be reduced to 0.75 mg/day in case of tolerable side effects. If patients could not tolerate the dosage of 0.75 mg/day, they were terminated from the study.

To exclude diagnosis of co-morbid current axis I disorders, all subjects were assessed at baseline using the Mini International Neuropsychiatric Interview [41]. The Clinical Global Impression Scale (CGIS) [42], a Visual Analogue Scale to assess the craving [43] and a self-report questionnaire on the use of cocaine were administered at baseline and then weekly throughout the study.

In order to monitor the use of cocaine and other substances (cannabis, morphine, methadone and amphetamines) during the study, urinalyses were carried out three times per weeks during the study at the Drug Addiction Services to search for metabolites.

Urine samples were analyses using immunoenzymatic procedures (competitive enzyme donor immunoassay, CEDIA). Samples exceeding the cut-off of 300 ng/ml of benzoylecgonine were considered positive [44].

In order to determine the safety of the study, drugs vital signs were examined weekly and laboratory tests (blood count, renal and liver function blood tests, creatine-phosphokinase, glucose and lipid profiles) were carried out at baseline and at endpoint.

No psychotherapy was carried out during the study because of its potential confounding effect.

The study protocol was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria of Pisa (the coordinating centre) and by the Ethics Committees of the other participating centres. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants signed a written informed consent after receiving a description of the study and having an opportunity to ask questions.

Statistical Analysis

The outcomes of interest were: craving intensity, CGI improvement at end point, mean weekly consumption of cocaine (in grams), mean number of weekly administrations of cocaine and positive urine samples.

The proportions of completers and of visits attended were compared between the two study groups using the χ^2 test.

The proportion of positive urine samples was compared between groups using the M-W test both in the ITT sample (i.e. randomized patients), and in study completers.

Clinical improvement at end point was compared between the two groups using the Mann-Whitney (M-W) test.

The treatment efficacy on craving, cocaine consumption and cocaine administration was analyzed using linear mixed-effects models for multilevel longitudinal data; each outcome was considered separately as dependent variable. In the fixed-effects component of the model, the following sources of variation were investigated: treatment (aripripazole or ropinirole), time, and their interac-

tions. The random effects component of the model allowed for between-patient random heterogeneity in the effects of treatment and of the interaction between treatment and time. The model estimates the regression coefficient (a measure of the mean effect) with 95% confidence intervals and a random slope (representing deviation from the mean, i.e. the regression coefficient for each patient) for any variable in the fixed or random components of the mixed-effects model. For all patients, the model summarizes random coefficients with their standard deviations, which represent a measure of interindividual variability.

The overall significance of the introduction of the random component of the model was evaluated using the log-likelihood ratio test. The models were fitted using maximum likelihood estimation.

Analyses were carried out using SPSS, version 17.0 and STATA/IC 10.1.

RESULTS

Thirty patients were screened for potential participation. Two of them refused to participate, 16 were randomized to aripiprazole and 12 to ropinirole (see Patient flow). Participants included 22 men and 6 women, with a mean age of 33.4 years, SD=6.8, range 22-51; 75% were employed and 93% were living with their family or with their partner, 43% had more than 8 years of education (Table **1**).

Seven patients assigned to aripiprazole and 4 assigned to ropinirole were on methadone maintenance therapy. Urine analyses revealed occasional use of amphetamines in 1 patient on aripiprazole, regular use of cannabis in 3 patients on aripiprazole and occasional use in 1 patient on aripiprazole, occasional use of morphine in 2 patients on aripiprazole and 2 on ropinirole and regular use of morphine in 2 patients on aripiprazole.

Fourteen patients completed the study (9/16 in the aripiprazole and 5/12 in the ropinirole group, χ^2=0.58, p=0.44) and 14 failed to complete the protocol (see Consort Diagram). Of these, 7 discontinued treatment (3 ropinirole, 4 aripripazole) and other 7 were terminated from the study from the clinicians (4 ropinirole, 3 aripiprazole). In none of these patients treatment discontinuation was related with side effects.

Reasons for protocol discontinuation included patients' difficulties going daily to the Drug Addiction Service to take treatment for job reasons (N=5) or without justification (N=2). Reasons for termination from clinicians included non-compliance (N=2), admission to a residential facility (N=2), hospitalization for reasons unrelated to drug dependence (N=1), incarceration (N=1), myocardial infaction related to acute cocaine intoxication (N=1).

The overall proportion of visits completed did not differ between the two study groups (70.3% in the aripiprazole group and 68.7% in the ropinirole group, χ^2 =0.09, p=0.758).

Safety and Tolerability

Ropinirole was titrated to 1.5 mg/day in all but 1 patient, who had a stable dosage of 0.75 throughout the protocol. One patient required a dosage reduction from 1.5 to 0.75 mg after one week of treatment because of sleepiness.

Aripiprazole was titrated to 10 mg/day in all patients and was well tolerated. Only one patient reported moderate akathysia at visit 3 and had the dosage reduced to 5 mg/day.

Routine blood works did not show significant changes from baseline, when repeated at the 4th, 8th and 12th weeks of treatment.

Severity and Improvement

The CGI severity score at baseline was 4.6 (SD 1.5) in the aripiprazole and 4.8 (SD 1.1) in the ropinirole group, without significant differences (M-W Z test=-0.116, p=0.936). In patients completing treatment, the mean severity score at endpoint was 3.0 (SD 1.5) in the aripiprazole and 3.4 (SD 1.8) in the ropinirole group (M-W Z-test=-0.253, p=0.876).

Starting from visit 3, patients exhibited mild to moderate improvement. Median improvement at endpoint was moderate in the aripiprazole group and mild in the ropinirole group, but this difference was not significant (M-W Z test=-0.420, p=0.755).

Craving and Cocaine use

The intensity of craving, measured from 0 to 100 on a visual-analogue scale, decreased on average 35 percentage points (from 67.2±24.6 at baseline to 32.1±27.0 endpoint) in patients treated with aripiprazole, and 22 points in patients treated with ropinirole (from 69.2±24.6 to 47.0± 34.0). From baseline to endpoint the mean weekly cocaine use decreased from 6.2±8.0 g to 0.6±0.7 g in the aripiprazole group and 5.4±4.2 g to 1.8±1.0 g in the ropinirole group. The mean number of weekly administrations decreased from 1.4±1.6 to 0.1±0.1 (aripripazole) and from 1.1±0.8 to 0.3±0.2 (ropinirole).

The overall proportion of positive urinalyses for cocaine metabolites was higher in the aripiprazole group than in the ropinirole groups, but the difference was not significant both in the ITT sample (median aripiprazole=62, median ropinirole=42, M-W test Z=-0.472, p=0.637) and in the completer sample (median aripiprazole=51, median ropinirole=28, M-W test Z=-1.069, p=0.285 - Fig. **4**).

Linear Mixed-effect Model Results

The analysis of data using linear mixed effect-models showed a significant decrease in craving in the overall sample (p<0.001) (Table **2**). However, the slopes did not differ between the two treatments (Fig. **1**). The mean consumption of cocaine decreased in both groups without reaching statistical significance (p=0.068) (Fig. **2**). Of note, the mean number of cocaine administrations exhibited a faster decrease with aripiprazole compared with ropinirole (p=0.009) almost reaching 0 after 12 weeks of treatment (Table **2** and Fig. **3**). All random-effects models proved to be better than the models with fixed effects, with a significant decrease in the log-likelihood. This confirms the large between-subjects variability.

DISCUSSION

The results of the present study indicate that aripiprazole and ropinirole are safe in patients with cocaine dependence at the study dosages of 5-10 mg per day and 0.75-1.5 mg per day, in line with the literature [37, 45].

Both treatments were well-tolerated and no patient dropped out because of side effects. Nobody requested to increase dosage throughout the 12-week period, suggesting an absence of tolerance to aripiprazole and ropinirole effects [30, 46].

Results of routine blood works did not demonstrate signs of toxicity, confirming the safety of aripiprazole and ropinirole. Still, the retention rate was low (9/16, 56.2% aripiprazole; 5/12, 41.7% ropinirole). In the review of de Lima *et al.* [3], retention rates in pharmacological studies of cocaine dependence were even lower when patients with psychiatric comorbidity were included.

The socio-demographic characteristics of the study sample are consistent with those reported in other papers on pharmacotherapy for cocaine abuse, such as gender distribution, marital status and education [47-49], without significant differences of the CGI severity score at baseline between the aripiprazole and ropinirole groups.

Although the open-label nature of the study and the small number of patients enrolled constitute important limitations, our results indicate that craving decreases significantly with both treatments, but aripiprazole seems to be more effective, producing a significantly higher reduction in the mean number of cocaine administrations than ropinirole after 12 weeks of treatment. These effects cannot be accounted for psychotherapy or other social interventions

Table. 1. Characteristics of the Study Sample by Treatment Assignment

	Aripriprazole		***Ropinirole***	
	N=16		**N=12**	
Gender	N	%	N	%
Male	12	75.0	10	83.3
Female	4	25.0	2	16.7
Age (years)	33.5± 6.1		33.2±8.0	
Nationality				
Italian	16	100.0	11	91.7
Missing	0	0.0	1	8.3
Marital status				
Single	10	62.5	6	50.0
Married	3	18.8	2	16.7
Separated	0	0.0	1	8.3
Living with partner	3	18.8	2	16.7
Missing	0	0.0	1	8.3
Educational level				
<5 years	1	6.3	0	0.0
Primary school	0	0.0	1	8.3
Secondary school	9	56.3	5	41.7
High school	5	31.3	6	50.0
University degree	1	6.3	0	0.0
Living arrangement				
Alone	1	6.3	1	8.3
With parents	7	43.8	4	33.3
With partner	2	12.5	5	41.7
With spouse and children	5	31.3	2	16.7
With other relatives	1	6.3	0	0.0
Working status				
Unemployed	3	18.8	3	25.0
Employed	8	50.0	7	58.3
Self-employed	5	31.3	0	0.0
Part-time work	0	0.0	1	8.3
Other (student, retired)	0	0.0	1	8.3
Legal situation				
No criminal record	9	56.3	9	75.0
Entrusted to social services	2	12.5	0	0.0
Criminal record	1	0.0	2	16.7
Awaiting trial	4	6.3	1	8.3

Table. 2. Effects of Covariates on Cocaine Craving, Mean Weekly Consumption and Mean Weekly Administrations of Cocaine

Covariate	Craving		Weekly consumption (grams)		Weekly administrations	
	Regression coefficient (95% CI)	Z, p-value	Regression coefficient (95% CI)	Z, p-value	Regression coefficient (95% CI)	Z, p-value
Time	-3.59 (-5.12 to -2.04)	<0.001	-0.23 (-0.49 to 0.02)	0.068	-0.03 (-0.08 to 0.01)	0.110
Treatment	-3.62 (-23.9 to 16.6)	0.726	0.07 (-2.44 to 2.59)	0.956	0.29 (-0.34 to 0.92)	0.367
Time X treatment	0.49 (-0.55 to 1.54)	0.354	-0.14 (-0.47 to 0.18)	0.384	-0.07 (-0.13 to -0.02)	0.009
constant	65.81 (38.51-93.11)	<0.001	4.32 (2.41 to 6.22)	<0.001	0.88 (0.40 to 1.36)	<0.001

Fig. (1). Cocaine craving, measured on a VAS scale (0-100).

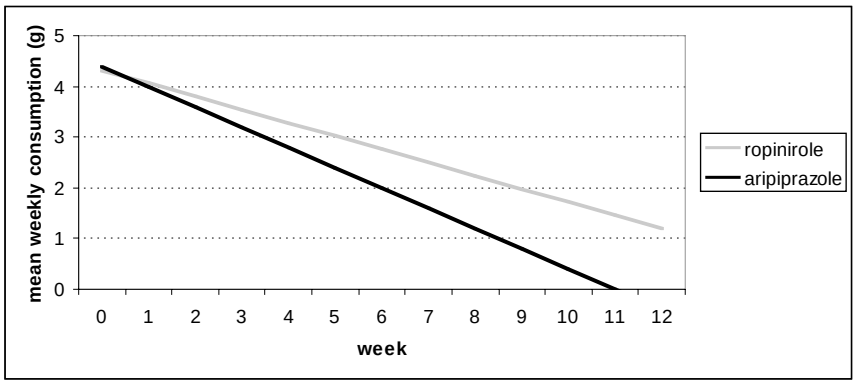


Fig. (2). Mean weekly consumption of cocaine.

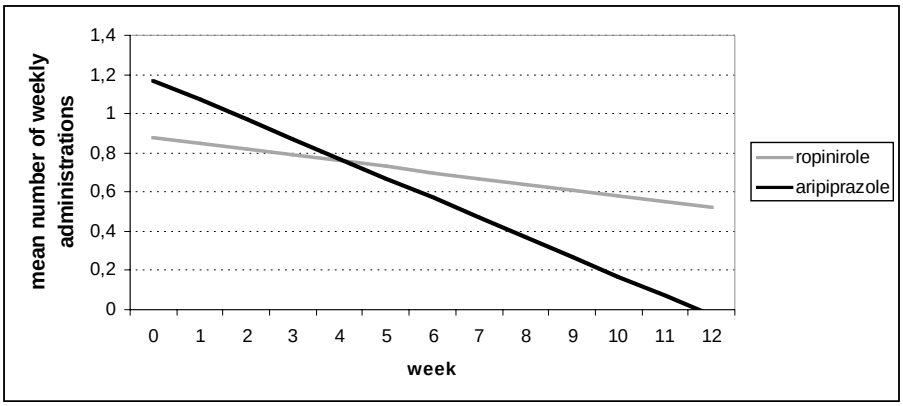


Fig. (3). Mean number of weekly cocaine administrations during the study.

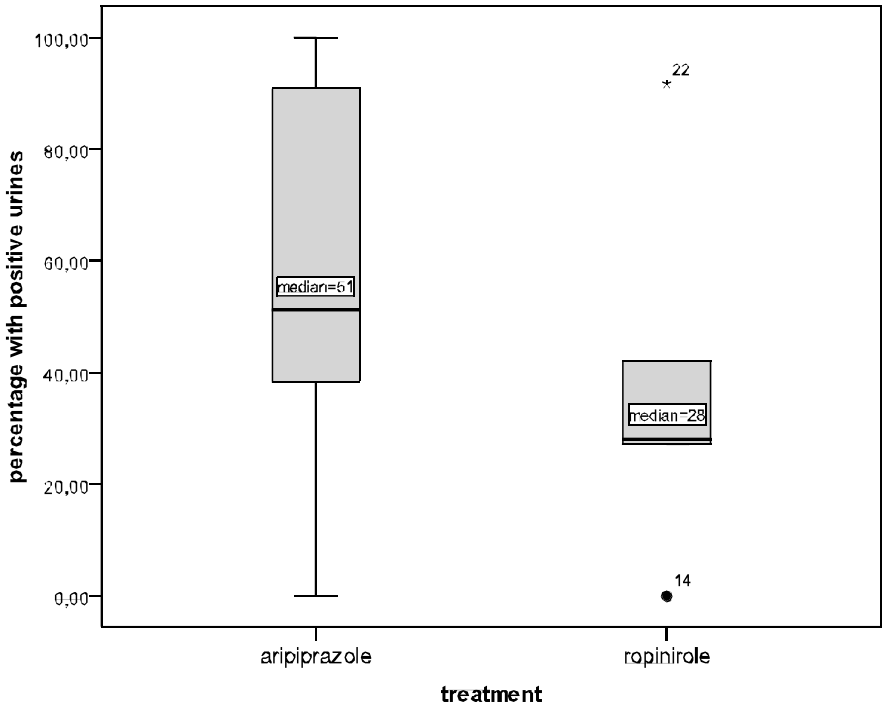
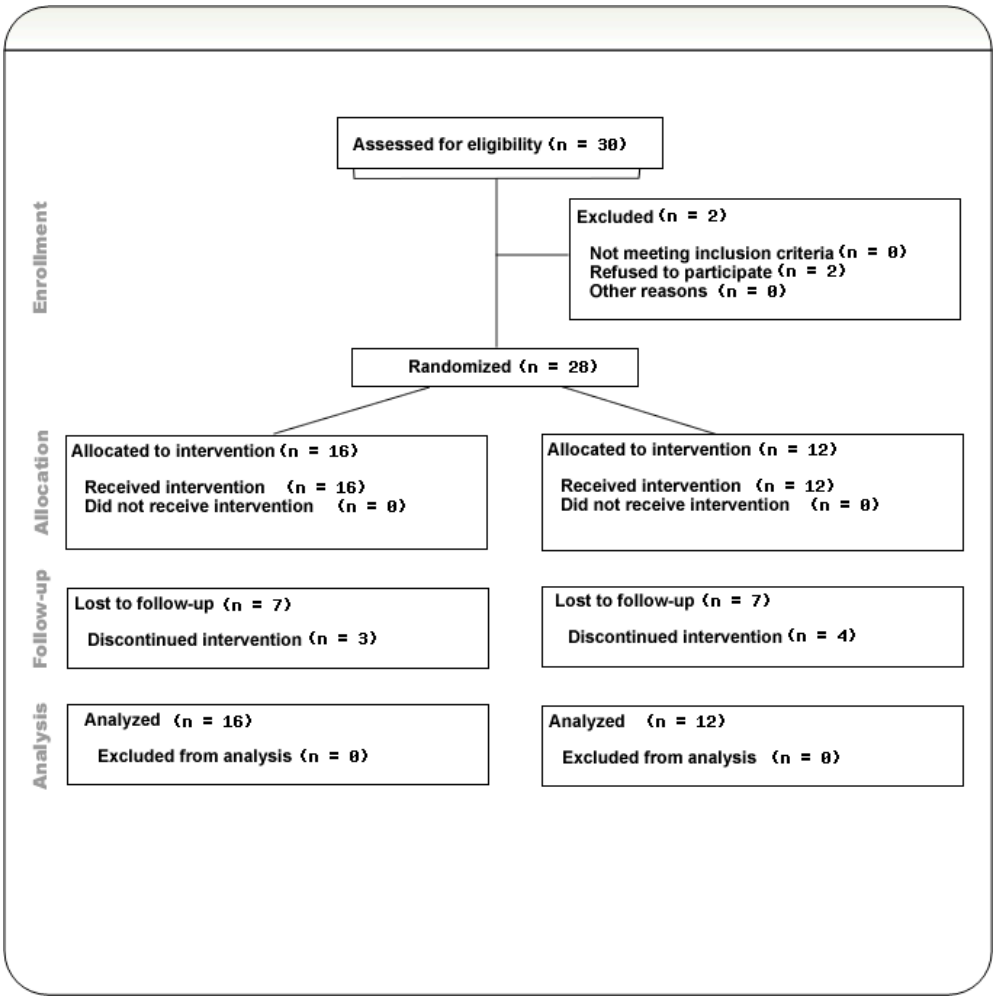


Fig. (4). Percentage of positive urines in the completer sample.



Patent Flow.

because these treatments were not offered during the study. However, in the absence of a placebo group we cannot exclude that the effects observed can be ascribed to the general effects of being in a treatment setting. Still, our results are consistent with existing evidence on ariprazole efficacy in reducing cocaine craving. Moreover, this pilot study provides useful information on the retention rates and the effects of aripiprazole and ropinirole treatments, to be used for planning larger clinical trials on treatment for cocaine dependence.

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