

Long-Acting Injectable Risperidone Compared With Zuclophenthixol in the Treatment of Schizophrenia With Substance Abuse Comorbidity

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Objective: This study aimed to compare the efficacy of long-acting risperidone and zuclophenthixol in subjects with schizophrenia and substance abuse.

Method: A total of 115 subjects with schizophrenia and substance use disorders were enrolled for an open, randomized, controlled, 6-month follow-up study. Fifty-seven subjects were selected for treatment with long-acting injectable risperidone, while another 58 were treated with zuclophenthixol-depot.

Results: Long-acting risperidone patients presented fewer positive urine tests (8.67 compared with 10.36, $P = 0.005$), showed improved scores on the Positive and Negative Syndrome Scale, and showed better compliance with the Substance Abuse Management program. The use of long-acting risperidone and less severe dependence explained the outcome at the end of the follow-up.

Conclusions: Long-acting injectable risperidone was more effective than zuclophenthixol-depot in improving substance abuse and schizophrenia symptoms in subjects with dual diagnosis.

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Clinical Implications

- Long-acting risperidone is more effective than zuclophenthixol-depot in improving substance abuse in subjects with schizophrenia.
- Long-acting risperidone improves the efficacy of a cognitive-behavioural program for managing substance abuse.
- Atypical antipsychotics could be the best pharmacologic strategy in the treatment of subjects with schizophrenia and substance abuse comorbidity.

Limitations

- The study had an open design.
- Results may not be generalizable to other clinical populations.
- We included subjects with family support.

Key Words: schizophrenia, substance use disorders, dual diagnosis, long-acting risperidone, zuclophenthixol

Drug abuse is highly prevalent in schizophrenia patients. An estimated 50% of subjects diagnosed with schizophrenia also present SUDs, compared with 12% of the general population (1). Cannabis, alcohol, and cocaine are the substances most commonly used by these patients (1,2). It is considered that substance abuse hastens the onset of schizophrenia, aggravates its symptoms, leads to poorer therapeutic compliance, and increases hospitalizations in this population (3,4). Despite high comorbidity and the impact of substance use on the outcome of schizophrenia, controlled studies assessing the effectiveness of pharmacologic treatment in this type of patient are rare (5). In 2 recent studies, risperidone decreased relapse for substances more than typical neuroleptics in subjects with schizophrenia and substance abuse (6–7). However, owing to compliance problems, many psychiatrists tend to prefer using depot neuroleptics to ensure better compliance and to reduce exacerbations and hospitalization in these patients (8,9).

Bearing in mind the scarcity of controlled studies in this field, we opted to carry out the first controlled study comparing long-acting injectable risperidone and zuclopenthixol-depot in subjects with schizophrenia and SUDs. Risperidone is an atypical antipsychotic widely used in the treatment of schizophrenia patients (10). It has been shown that long-acting injectable risperidone improves schizophrenia symptoms in stabilized patients treated with typical or atypical antipsychotics when switched to it (11). Zuclopenthixol is a well-established thioxanthene antipsychotic. Zuclopenthixol's controlled studies have shown that this antipsychotic is as effective as chlorpromazine (12) and risperidone (13) in the treatment of schizophrenia patients. It can be administered intramuscularly or orally.

The objective of the present study was to compare the efficacy of the 2 drugs in improving substance abuse in subjects with dual diagnosis. At the same time, we aimed through this comparison to determine which antipsychotic drug would improve schizophrenia symptoms and produce better compliance with the psychotherapeutic program for managing substance abuse.

Abbreviations used in this article

ASI	Addiction Severity Index
CI	confidence interval
ECG	electrocardiogram
ESRS	Extrapyramidal Symptom Rating Scale
SUD	substance use disorder
PANSS	Positive and Negative Syndrome Scale
SAMM	substance abuse management model
UKU	Udvalg for kliniske

Method

Chronic schizophrenia patients with SUDs were enrolled for a randomized, controlled study carried out at 2 outpatient centres in Spain. The study was performed in accordance with the Helsinki Declaration (1964) (see www.cirp.org/library/ethics/helsinki/). Approval of the protocol by appropriate local ethics committees was also secured. We obtained a written informed consent in all cases.

Patients

To be eligible for inclusion, patients were between the ages of 18 and 65 years, with a diagnosis of schizophrenia and SUD for substances other than caffeine and nicotine, according to the Structured Clinical Interview for DSM-IV (14). Patients were excluded from the study if they had a clinically significant organic or neurologic disorder, serious psychotic disorder other than schizophrenia, clinically relevant abnormalities in laboratory tests at baseline, neutropenia or thrombocytopenia, or a clinically relevant abnormal ECG.

Patients were selected during their stay in hospital. They had been admitted owing to a worsening of their psychotic symptomatology. Once stabilized, and before being discharged, they were asked if they would participate in the study. Of 183 patients interviewed, 115 agreed to participate.

Design

Patient selection took place while patients were in hospital. When informed consent was obtained, subjects were allocated alternately to receive long-acting injectable risperidone or zuclopenthixol-depot. They remained in hospital for an additional 7 to 15 days, until being referred to their outpatient centre to continue pharmacologic treatment for 6 months.

Before hospital discharge, patients were given a baseline interview. They had a weekly consultation with their psychiatrist, who was responsible for prescription and monitoring of the risperidone and zuclopenthixol and for the program to prevent substance use relapses. At each weekly visit, patients also took a urine test to check for alcohol, opiates, cocaine, and cannabis (InstaCheck Drug Screen Test, Applied Biotech/Forefront Inc, San Diego, CA).

Every 2 months, subjects were interviewed by a monitor with no knowledge of their pharmacologic treatment, until the 6-month follow-up period was complete (total 24 weeks).

Patients could ask to drop out of the study at any time. Failure to attend the interviews or to take the urine test during follow-up was not considered sufficient reason to exclude subjects from the study. Patients who had to be admitted to a psychiatric hospital during the follow-up period were given the opportunity of continuing the study if they wished. If the patient failed to attend the bi-monthly visit (for example, because he

or she was hospitalized), the interview was postponed until it was possible for the patient to attend.

Justification of the Design

We chose an open design to avoid the typical complications that may arise in double-blind studies with substance abusing patients. The emergence of adverse reactions and (or) severe side effects may lead blind researchers to exclude the patient from the study when, in many cases, secondary reactions to substance use are involved.

To avoid the possible bias resulting from assessment of the patient by the clinician (who was obviously aware of the treatment prescribed), we opted to include blind assessors. We used a long follow-up period in view of the fact that changes of habit related to substance use are difficult and take considerable time. Thus the conditions of the study are as close as possible to those of normal practice.

Blind Researchers

The outcome data were collected by researchers who were blinded to the drug taken by the patients. Every 2 months, they interviewed subjects and filled out the different efficacy and safety scales.

Assessment Instruments

Evaluation of SUDs and use of substances. Although patients were asked about substance use in each of the interviews, we included detection of substances in urine as measures of substance-use assessment in the weekly tests. Reactive strips were used for alcohol, cocaine, opiates, and cannabis (Instacheck, San Diego, CA). Severity of the complications of substance use was assessed by the Addiction Severity Index (15).

Evaluation of Efficacy on Schizophrenia Symptoms. Efficacy was assessed with the PANSS (16) for schizophrenia and the Clinical Global Impression scale (17).

Evaluation of Safety. Extrapyramidal symptoms were evaluated with the ESRS (18). The effects of other adverse events on the patients' daily activities were evaluated by means of the UKU Side Effect Rating Scale (19).

Psychotherapeutic Program

Roberts and colleagues (20) developed the SAMM program, which comprises the following modules: basic training (8 sessions), skills training (9 sessions), and practical sessions. It is based on a cognitive-behavioural approach and is designed specifically for patients diagnosed with schizophrenia and substance abuse. All the subjects attended this type of psychotherapeutic session weekly until the completion of 24 sessions.

Outcome Variables

The main outcome variable was the number of positive urine tests during the follow-up period. Time elapsed before the first positive urine test was also evaluated.

The secondary outcome variables were:

1. Reduction in the scores of the different subscales of the PANSS. We considered as therapeutic efficacy a reduction of at least 20% in the total PANSS score with respect to the baseline situation.
2. Compliance with the SAMM program, determined by the number of times participants attended the program sessions during the study. Compliance was considered to be adequate when subjects attended 18 sessions or more during the follow-up (75% of sessions).

Statistical Analysis

Measures of efficacy and safety were analyzed according to the intent-to-treat principle. Unpaired *t* tests were used to analyze differences between treatment groups. Dichotomous variables were evaluated with Pearson's chi square test or 2-tailed Fisher's exact test. Variations in each of the variables in a given treatment group were analyzed with 2-tailed paired *t* test. We used a last observation carried forward model for repeated-measures analysis and employed a significance level of 0.05 to characterize the results. We determined the number of patients with negative urine tests at the end of Month 6 with the Kaplan-Meier product-limit survival test. We used different regression models to explain the clinical response to substance use (two-thirds of the urine controls were negative), clinical response of the psychopathology (PANSS total < 20% of baseline), and compliance with the psychotherapeutic program (75% attendance at sessions) at the end of the follow-up period.

Results

The demographic and baseline characteristics did not differ significantly between the 2 treatment groups (Table 1). Patients were treated with oral neuroleptic drugs prior to commencement of the trial (haloperidol 80% and chlorpromazine 20%).

During the follow-up period, 9 of 115 patients dropped out of the study, 6 from the zuclophenthixol-depot group and 3 from the long-acting risperidone group. Five of these were rehospitalized and spent 6 months as inpatients. The other 4 did not agree to attend the program for the management of substance abuse. Ten of 57 patients from the long-acting risperidone group and 11 of 58 subjects from the zuclophenthixol-depot group needed to be admitted to a psychiatric hospital during this period owing to exacerbation of their psychopathological symptoms. At the end of the follow-up, the risperidone group was treated with 47.2 mg per 15 days of long-acting risperidone and 3.4 mg daily (range 2 mg to 6 mg) of oral risperidone. The zuclophenthixol group was also receiving 200 mg of zuclophenthixol-depot every 21 days and a daily oral dosage of 15 mg (range 10 mg to 50 mg).

Table 1 Demographic and clinical characteristics of treatment groups

	Risperidone <i>n</i> = 57	Zuclophentixol <i>n</i> = 58	<i>P</i>
	<i>n</i> (%)	<i>n</i> (%)	
Diagnosis according to DSM-IV			0.96
Paranoid	29 (50)	31 (53.4)	
Residual	12 (21.0)	10 (17.2)	
Undifferentiated	8 (14.0)	9 (15.5)	
Disorganized	8 (14.0)	8 (13.7)	
Positive family history for			
Schizophrenia	16 (28.0)	14 (24.1)	0.62
SUD	19 (33.3)	20 (34.4)	0.89
	Mean (SD)	Mean (SD)	
Age (years)	37.90 (8.66)	33.45 (9.46)	0.14
Age at onset of diagnosis	21.19 (4.71)	20.75 (4.80)	0.61
Age at first hospitalization	23.12 (4.80)	23.13 (6.41)	0.99
Number of hospitalizations	7.1 (6.50)	6.80 (6.60)	0.76
PANSS positive	22.71 (7.2)	22.0 (8.0)	0.59
PANSS negative	25.96 (9.4)	26.74 (8.7)	0.64
PANSS general	45.12 (10.2)	45.50 (11.0)	0.85
Baseline PANSS total score	93.79 (22.9)	93.69 (22.5)	0.98
ASI			
Medical	2.4 (2.86)	2.18 (2.55)	0.68
Work	4.54 (3.28)	5.15 (2.86)	0.60
Alcohol	5.25 (4.12)	4.58 (4.15)	0.59
Other substances	6.19 (3.22)	6.48 (2.95)	0.80
Legal	0.64 (1.78)	0.79 (1.96)	0.67
Financial	4.96 (3.42)	5.33 (2.75)	0.57
Psychological	8.05 (2.07)	8.42 (1.41)	0.70
SUD			
Nicotine, <i>n</i> (%)	41 (71.9)	40 (68.9)	0.72
Cigarettes daily, mean (SD)	24 (7.2)	25 (6.7)	
Alcohol, <i>n</i> (%)	50 (87.7)	51 (87.9)	0.97
Drinks weekly, mean (SD)	52 (8.1)	50 (9.2)	
Cannabis, <i>n</i> (%)	40 (70.2)	42 (72.4)	0.79
Cigarettes weekly, mean (SD)	29 (6.3)	30 (7.2)	
Cocaine, <i>n</i> (%)	14 (24.5)	16 (27.5)	0.71
g weekly, mean (SD)	0.8 (0.5)	0.7 (0.6)	
Opiates, <i>n</i> (%)	6 (10.5)	4 (6.8)	0.49
mg weekly, mean (SD)	120 (75)	100 (90)	
MDMA, <i>n</i> (%)	2 (3.5)	3 (5.1)	0.63
Pills weekly, mean (SD)	2.4 (1.4)	2.2 (1.6)	

Equivalences: 1 drink = 10 g ethanol, 1 cannabis cigarette = 1–2 Euros; 1 g street cocaine = 36–60 Euros, 100 mg street heroin = 2–4 Euros, 1 pill of MDMA = 3–6 Euros

Table 2 Results of clinical assessments during 6-month follow-up

Assessment	Long-acting risperidone (n = 57)	Zuclopenthixol-depot (n = 58)	P
	Mean (SD)	Mean (SD)	
Substance abuse			
Average number of tests performed during the period of study (per subject)	19.70 (2.83)	17.61 (3.96)	$t = 3.26$, df 113; $P = 0.001$
Average positive tests during the period of study (per subject)	8.67 (3.0)	10.36 (3.1)	$t = 2.31$, df 113; $P = 0.005$
Relapsers	57(100)	58(100)	
Efficacy on psychopathology (evaluation at 6 months)			
PANSS Positive	13.76 (6.19)	15.02 (7.50)	$t = -0.53$, df 104; $P = 0.59$
PANSS Negative	18.80 (8.71)	23.81 (7.40)	$t = -2.69$, df 104; $P = 0.008$
PANSS General	32.02 (9.71)	37.62 (11.82)	$t = -2.06$, df 104; $P = 0.05$
PANSS total	64.93 (19.9)	74.03 (20.9)	$t = -2.36$, df 104; $P = 0.02$
Safety (evaluation at 6 months)			
ESRS	1.24 (0.3)	2.85 (1.1)	$t = -2.08$, df 104; $P = 0.05$
Compliance			
Average of program sessions attended (per subject)	19.70 (2.83)	17.61 (3.9)	$t = 3.26$, df 113; $P = 0.001$
Compliance ^a			
Good (subjects classified as compliers), %	92.91	67.79	$\chi^2 = 14.27$, df 1; $P = 0.001$

^aGood compliance: >75% of the sessions

Substance Abuse

The number of positive urine tests was significantly higher in the zuclopenthixol group than in the risperidone group (Table 2). All patients consumed substances during the follow-up, even though the first positive urine test occurred in the ninth week for the long-acting risperidone group (95%CI, 7 to 10) and the seventh for the zuclopenthixol group (95%CI, 5 to 8) (Longrak 2.86, df 1, $P < 0.09$) (Figure 1).

Psychopathology

There were significant differences in the Negative and General Psychopathology PANSS subscales at the end of the study (Table 2). The percentage of subjects with a PANSS score 20% lower than that of baseline was higher in the group treated with risperidone (89% and 50%; $\chi^2 = 21.1$, df 1, $P < 0.0001$).

Compliance

Patients treated with risperidone attended a significantly larger number of SAMM program sessions than those of the zuclopenthixol group. In fact, 92.9% of those in the risperidone group were classified as good compliers (Table 2).

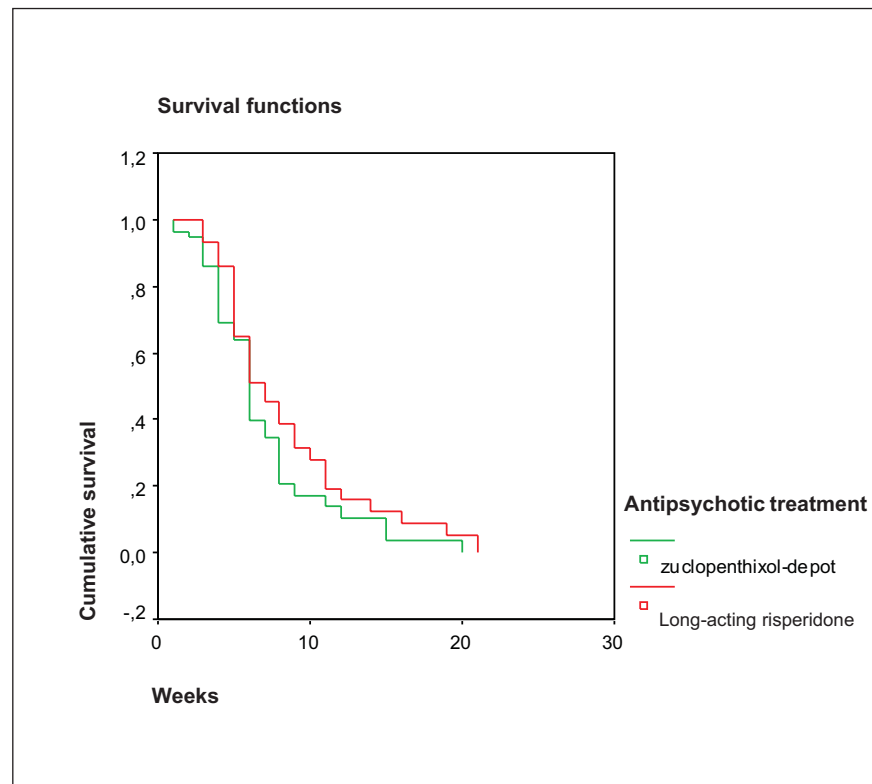
Drug Safety

There was a more significant reduction in the scores on the scales for EPS and UKU ($t = 1.92$, $P < 0.04$) in the risperidone group. Antiparkinsonian drugs were used more frequently in the zuclopenthixol group (48.5% and 27%, $\chi^2 = 5.69$, df 1, $P < 0.01$).

Logistic Regression Models for Explaining the Prognosis

In the model for explaining the reduction in positive urine tests, the variables involved at the end of the follow-up period were severity of dependence measured with the ASI and type of antipsychotic received during the treatment. That is, greater reduction in positive urine tests was associated with having used long-acting risperidone and with less severity of dependence.

Regarding the model for explaining the reduction of the total PANSS score by > 20%, at the end of follow-up, the variables that entered the model were baseline severity of dependence measured with the ASI and type of treatment received during the study. That is, the less severe the dependence, the higher the risk of a reduction in the total PANSS score.

Figure 1 Survival analysis for positive urine tests

Finally, in the model for explaining compliance with the SAMM program, the variables involved were number of hospitalizations since onset of schizophrenia, type of antipsychotic received during the study, and severity of dependence measured with the ASI. It might therefore be stated that a history of few admissions to a psychiatric hospital, using long-acting risperidone, and less severe dependence, is associated with better compliance.

Discussion

The results of this study indicate that, in subjects with schizophrenia and substance abuse, long-acting risperidone was more useful than zuclopenthixol-depot in reducing substance abuse and in alleviating symptomatology of schizophrenia. Risperidone also led to more improvement than zuclopenthixol with regard to compliance with the program for managing substance abuse. Taking into account the results of the different regression models, it can be stated that choice of antipsychotic is relevant for explaining the results related to substance abuse and schizophrenia symptoms and to compliance with the psychotherapeutic program.

With regard to the reduction in substance use, the results of the present study indicate that long-acting risperidone contributes to reducing substance consumption in a consistent way,

mainly in subjects with less severe dependence. Also, in a previous study (6), risperidone decreased positive urinary tests significantly more than zuclopenthixol in subjects with schizophrenia and SUDs. Smelson and others showed that individuals with schizophrenia and cocaine dependence treated with risperidone had significantly fewer cue-elicited cravings and relapses than did subjects treated with typical antipsychotics (7). Indirect evidence of the greater efficacy of risperidone can be found in other studies. Where it has been used in the treatment of subjects with psychotic disorders and opiates abuse, it has been shown that 50% of subjects reduced their use of opiates (21).

Indeed, it has been speculated that this type of antipsychotic may form the basis of the principal treatment strategy for acting on negative symptoms and reducing dysphoria and extrapyramidal symptoms (5). There are several nonexclusive hypotheses that support this notion. It has been pointed out that patients diagnosed with schizophrenia tend to use substances more frequently than the general population in an attempt to reduce their states of dysphoria (22,23), the positive and negative symptoms of the disorder (22-26), and the cognitive deficits related to schizophrenia or psychoactive drugs (27) or in an attempt to increase mesocortical dopaminergic hypoactivity and alleviate the anhedonia

Table 3 Logistic regression models for explaining the outcome variables

Outcome variables	Odds ratio (95%CI)	P
At least 2 of 3 urine drugs tests negative		
Having been treated with long-acting risperidone	4.71 (1.57–14.1)	0.005
Severity of the dependence measured on ASI	1.18 (1.06–1.30)	0.001
Reduction in PANSS-total > 20%		
Having been treated with long-acting risperidone	11.4 (3.89–33.5)	0.0015
Severity of the dependence measured on ASI	1.15 (1.05–1.26)	0.001
Attendance at 75% of SAMM program sessions		
Having been treated with long-acting risperidone	13.2 (3.2–5.4)	0.0003
Number of hospitalizations since disorder onset	1.12 (1.03–1.22)	0.005
Severity of the dependence measured on ASI	1.09 (0.99–1.20)	0.06

associated with their situation (28). It is also possible that a subgroup of these patients will present greater risk owing to the presence of antisocial features or novelty seeking, modulated by the serotonergic and dopaminergic systems, respectively (5). The pharmacologic characteristics of atypical antipsychotics and, in particular, risperidone, and their actions on factors of vulnerability to substance use in this population may partly explain their efficacy (5). Moreover, outside the context of patients diagnosed with schizophrenia, it has been suggested that atypical antipsychotics may reduce the use of such substances as alcohol and cocaine (29,30). It has been hypothesized that atypical antipsychotics reduce substance use more than classic neuroleptics owing to lower hypersensitivity to D₂ dopaminergic receptors in mesolimbic pathways (31,32).

In relation to the efficacy of long-lasting risperidone and zuclopenthixol-depot in reducing schizophrenia symptoms, it is not possible to compare similar studies. However, the differences between the 2 drugs in schizophrenia subjects have been pointed out elsewhere (6,13). In samples with and without dual diagnosis, risperidone and zuclopenthixol were equally effective in reducing positive, but not negative, symptomatology. The percentage response to long-acting risperidone in our study (89%) is higher than others found in those carried out in subjects with schizophrenia and SUD (72%, 6) or without SUD (61% to 74%, 33–35). However, percentage response to zuclopenthixol-depot was also higher than in other studies (44–48%; 6,13). The greater efficacy of risperidone, compared with zuclopenthixol, above all in the reduction of negative symptoms, may be explained by the different pharmacologic actions of the 2 drugs (36,37).

Regarding program compliance for managing substance use, the results are better than others shown in a previous study (6). It has been suggested that one of the possible determining

factors in the achievement of medium- and long-term objectives is that patients with less severe dependence find the treatment program useful and that their clinical situation allows them to comply with and accept the content of the therapeutic program (6). Thus a pharmacologic treatment such as risperidone may be more effective than classic neuroleptics in achieving compliance with the psychotherapeutic program for 2 reasons: it reduces some of the clinical factors that may predispose to the use of drugs (positive and negative symptoms), and it reduces the reinforcing capacity of drugs of abuse. Thus patients may experience a greater sense of self-efficacy as they attain partial goals, which in turn would lead to more active involvement in the program. In subjects with more severe dependence, differences between treatments could disappear owing to the substance abuse effects.

In sum, there is a need for further research that would permit clinicians to approach more effectively the treatment of schizophrenia patients with dual diagnosis. It would also be of interest to determine which type of psychotherapeutic intervention is most appropriate for each type of patient and which works best in combination with the pharmacologic treatment.

The results of this study should be considered in view of the limitations. We excluded 37% of the subjects in the selection period. It may well be that precisely those most severely affected, in relation to both their psychotic condition and substance abuse, were the ones who declined to participate. Further, all participants were able to be treated as outpatients, which implies that they had at least some sort of family support. Those who were homeless or with inadequate social or family support (and who constitute a group with more serious characteristics) remained outside the study. The fact that the psychiatrists who treated the patients had knowledge of their outcome may also affect the results.

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Résumé : La rispéridone injectable à action prolongée contre le zuclopenthixol dans le traitement de la schizophrénie avec comorbidité d'abus de substance

Objectif : Cette étude visait à comparer l'efficacité de la rispéridone à action prolongée à celle du zuclopenthixol chez des sujets souffrant de schizophrénie et d'abus de substance.

Méthode : Un total de 115 sujets souffrant de schizophrénie et de troubles induits par une substance ont été inscrits dans une étude ouverte, randomisée, contrôlée avec suivi de 6 mois. Cinquante-sept sujets ont été choisis pour le traitement à la rispéridone injectable à action prolongée, tandis que les 58 autres ont été traités au zuclopenthixol-retard.

Résultats : Les patients du groupe de la rispéridone à action prolongée présentaient moins d'analyses d'urine positives (8,67 comparé à 10,36; $P = 0,005$), ils ont amélioré leurs scores à l'échelle de syndrome positif et négatif, et ils montraient plus d'observance du programme de traitement de la toxicomanie. L'utilisation de rispéridone à action prolongée et la dépendance moins grave expliquaient le résultat au terme du suivi.

Conclusions : La rispéridone injectable à action prolongée était plus efficace que le zuclopenthixol-retard pour améliorer les symptômes d'abus de substance et de schizophrénie chez les sujets ayant le double diagnostic.