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Ecstasy-Induced Psychotic Disorder: Six-Month Follow-Up Study

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Key Words

Drug-induced psychotic disorder · Ecstasy · Symptoms · Atypical neuroleptics · Olanzapine

Abstract

Objective: To describe the psychiatric symptoms manifested by persons diagnosed for the first time as having ecstasy-induced psychotic disorder and to explore the evolution of their symptoms over a 6-month period. ***Design:*** Observational study with a 6-month follow-up. ***Method:*** The subjects studied were 32 ecstasy consumers who were treated at two drug-dependency outpatient centers for hallucinatory-delusive manifestations and who were diagnosed as having ecstasy-induced psychotic disorder according to DSM-IV criteria. For the assessment of the intensity of the syndrome and its follow-up, the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression (CGI) were used at the outset and after 1, 3 and 6 months. All subjects received treatment with olanzapine. ***Results:*** The treatment program was completed by 96.9% of the patients. At the baseline assessment, a high incidence of symptoms of a severe psychiatric disorder was observed. From the first month the psychotic symptoms (BPRS) were considerably reduced with treatment, with the most severe positive symptoms remitting in the first 3 months. The three assessment indicators (BPRS, HDRS and CGI) showed a statistically significant clinical reduction over the 6 months of the assessment period. Furthermore, no relevant side effects were noted. ***Conclusions***: In its initial manifestations, a drug-induced psychotic syndrome includes marked symptoms meeting the criteria of a severe psychotic disorder, with the presence of considerable positive and negative symptoms. Olanzapine has been shown to be very effective in these situations and its use is suggested as first-choice therapy.

Introduction

Since the end of the 1980s, the biomedical literature has included descriptions of various adverse reactions to derivatives of meta-amphetamine (including ecstasy), either of an organic nature [1–3] or as psychiatric complications [4–13]. Furthermore, it seems that methylenedioxymethamphetamine (MDMA), ecstasy, and other analogous substances have neurotoxic properties on serotoninergic and dopaminergic neurons in both animals [14–16] and humans [17–20].

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The psychiatric complications, which are most difficult to distinguish diagnostically and treat effectively with drugs after the use/abuse of MDMA, include the hallucinatory-delusional syndromes. Since 1986, cases have been described with this type of syndrome and the difficulties in treating these patients with typical neuroleptics [4–13, 21] have been highlighted. In addition, in psychiatric emergencies in our country (Spain) a high percentage of patients with a first psychotic outbreak have been diagnosed as having drug-induced psychosis [22, 23]. Nonetheless, there are still difficulties regarding the differential diagnosis of the first psychotic outbreak [24].

In connection with cannabis-induced psychoses, certain trials have pointed to the rapid onset of psychotic symptoms and a notable presence of positive symptoms [25], while other authors have reported that they have not encountered differences between the psychoses induced by cannabis and other psychotic disorders [26–28].

Olanzapine is a new antipsychotic drug, one of the so-called atypical antipsychotics, with a favorable tolerance profile, and it has been shown to be effective against both the positive and negative symptoms of schizophrenia [29]. In addition, it has been suggested that olanzapine should be considered as first-choice therapy in the first psychotic episode because of its advantages in both safety and efficacy [30].

The objective of the present trial is to describe the psychiatric symptoms presented by persons diagnosed for the first time as having ecstasy-induced psychotic disorder and to examine the evolution of their symptoms after treatment with an atypical neuroleptic (olanzapine).

Patients and Method

The subjects were 32 ecstasy-consumers selected from a total of 56 individuals presenting with hallucinatory-delusional symptoms after repeated consumption of ecstasy. All of the cases (n = 56) were handled at two drug abuse treatment centers belonging to the public health network in the Spanish Basque Country (Osakidetza or Basque Health Service). Of these cases, 33.9% (19/56) were referred by public health service professionals participating in prevention programs focussing on the consumption of stimulants on the street and commercial premises. In view of the presence of the hallucinatory-delusional symptoms, these professionals advised the individual concerned or friends accompanying the same to report to a specialist service in order to assess the situation. The other 37 persons came to the drug abuse treatment center on their own account (21 cases) or at the urging of their families (16 cases). The recruitment period lasted for 45 months.

All of the individuals (n = 56) were interviewed by a psychiatrist who drew up the patient's case history. With regard to psychiatric history, 6 had previously suffered from psychotic syndromes, 23.2% (13/56) had previously presented with a nonpsychotic psychiatric disorder, and 32.1% (18/56) had a history of psychiatric treatment in a close relative. The use of other substances was examined through questioning of the subject concerned, with consumption of cannabis and/or amphetamines being recorded in 30.3% (17/56) of cases, cocaine in 10.7% (7/56) and heroin in 5.3% (3/56). Given the objectives of this trial, the 6 subjects with a prior history of psychosis were eliminated from the sample, as were the 18 who used other substances apart from ecstasy.

The final sample comprised 32 individuals who only consumed ecstasy. They were diagnosed as having ecstasy-induced psychotic disorder with delusional ideas (292.11) or hallucinations (292.12) according to the diagnostic criteria of the DSM-IV [31]. In all cases, the psychotic syndrome was present between 3 and 8 weeks prior to the first assessment interview with the psychiatrist.

The sex distribution was 27 males (84.4%) and 5 females (15.6%), all of them unmarried, with the group's mean age being 22.47 (SD 2.75; range 18–27) years. Fifty percent of the subjects (16/32) were students, 34.4% (11/32) were employed, and 15.6% (5/32) were unemployed. Three individuals had completed primary school education, 9 had completed professional qualifications, and 5 were university graduates. Ten of the subjects (31.2%, 10/32) were taking secondary education or vocational training courses, and 18.7% (6/32) were attending university. The mean duration of MDMA consumption was 16.94 (SD 5.14; range 6–26) months, and consumption primarily occurred during weekends (between Thursday and Sunday) with a mean dose of 5.3 (SD 3.4; range 3–15) tablets/day.

Procedure

In view of the severity of the syndrome presented, pharmacological treatment was started after the assessment interview. For ethical reasons the possibility of creating an untreated control group was discarded. Psychiatric treatment consisted of the following: olanzapine 10–15 mg/24 h during the first months, and 5–10 mg/24 h during the next 5 months; furthermore, all patients received support therapy (counselling, advice on handling symptoms, coping with situations and stimuli related with the consumption of ecstasy, etc.) with a frequency of 1 session/week in the first month, 1 session every 15 days for the next 2 months, and once a month for the last 3 months.

All of the subjects were assessed on recruitment to the program by application of the following instruments: the Brief Psychiatric Rating Scale (BPRS) [32]; the Hamilton Depression Rating Scale (HDRS) [33], and the Clinical Global Impression (CGI) [34]. Follow-up assessment was done after 1, 3 and 6 months using the same strategy as in the baseline assessment, with additional comments on incidents during the treatment. Use of substances was not determined by means of biological testing and consumption incidence was recorded on the basis of information volunteered by the patients.

Instruments

BPRS. The BPRS [32] comprises 18 items aimed at evaluating the intensity, characteristics and changes in psychotic disorder manifestations during treatment. The intensity of each item is scored on a scale of 0–4 (0 = normality, absence of symptoms; 1 = doubtfully present or mild symptoms; 2 = symptoms present, moderate intensity; 3 = the alteration is severely manifested, and 4 = very severe manifestations of the symptoms). For the version used in our evaluation [35], the cutoff points according to the global score to determine the absence of disorder, mild disorder or 'probable case' and 'severe disorder' or 'certain case' are 0–9, 10–20 and 21 or more, respectively.

Table 1. Change in the symptomatic assessment indexes (BPRS and HDRS) and the Clinical Global Impression (CGI): MANOVA over 31 cases

		Mean (SD)	Mean difference t-paired comparison test	Multivariate test, F(3,28)	Within-subject effect, F(3,90)
BPRS	Baseline (T0)	33.10 (4.78)			
	1st month (T1)	16.71 (4.51)	T0–T1 16.39*		
	3rd month (T3)	9.55 (3.98)	T1–T3 7.16*		
	6th month (T6)	5.00 (3.14)	T3–T6 4.55*	428.06*	717.83*
HDRS	Baseline	21.97 (6.82)			
	1st month	11.94 (4.68)	T0–T1 10.03*		
	3rd month	6.45 (2.75)	T1–T3 5.48*		
	6th month	3.23 (1.65)	T3–T6 3.22*	69.93*	141.47*
CGI	Baseline	3.90 (0.75)			
	1st month	2.39 (0.50)	T0–T1 1.51*		
	3rd month	1.52 (0.51)	T1–T3 0.87*		
	6th month	1.16 (0.37)	T3–T6 0.35*	219.38*	282.03*

BPRS = Brief Psychiatric Rating Scale; HDRS = Hamilton Depression Rating Scale; CGI = Clinical Global Impression.

* $p < 0.001$.

HDRS. The HDRS contains 17 items that assess the severity of the symptoms during the preceding week. Eight items are assessed on a scale of 0–2 (absent, doubtful, present) and nine on a scale of 0–4 (absent, doubtful, mild, moderate and severe). Although it is not a diagnostic instrument, the following cutoff points have been proposed [36, 37]: 0–11 = minor or no depression; 12–18 = less than major depression; 19–24 = major depression, and 25 or more = severe depression.

CGI. The CGI measures the overall assessment of the patient's severity by the clinician using a seven-point scale (0 = not assessed; 1 = not at all ill; 2 = doubtfully (borderline) mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill, and 7 = most extremely ill). The follow-up interviews used the change scale, also with 7 points (0 = not assessed; 1 = much better; 2 = considerably better; 3 = somewhat better; 4 = unchanged; 5 = somewhat worse; 6 = considerably worse, and 7 = much worse).

Data Analysis

Data analysis and processing were effected with version 10 of the SPSS [38].

The global indices have been calculated for the BPRS and HDRS at the different assessment times. The null hypothesis of no difference over the four interviews (intra-subject effect) was verified using a multiple analysis of variance for repeated measures (MANOVA), and where the null hypothesis is rejected, the pairs of means have been compared using the t test with the comparison error rate being adjusted using the Dunn-Bonferroni procedure [39]. In addition, the percentage of change was calculated for the variations in the scores at 1, 3 and 6 months with respect to the baseline score for each of the indicators used. This percentage of change was estimated by means of the following algorithm: [1 – (follow-up score/baseline score)] × 100.

Finally, since the objective of our study is to describe the expression of symptoms related to an ecstasy-induced psychotic disorder, an estimate was made for the percentage of subjects presenting notable symptomatic intensity (values ≥ 2, out of a range of 0–4) for each of the BPRS symptoms. The possible subscales derived from the grouping of different items in the BPRS [40, 41] were not calculated.

Results

Only 1 of the 32 subjects studied failed to conclude the follow-up period and abandoned the treatment visits in the third month.

Five subjects admitted to having consumed ecstasy at some point during the follow-up: 1 subject referred to consumption on three different occasions while the other 4 mentioned only one occasion each.

After treatment with olanzapine was begun, there were signs of mild akathisia in 1 case during the first month, mild dystonia in 1 case during 2 weeks and weight gain in 6 cases over the 6 months. In no case was it necessary to withdraw the drug under investigation or to associate it with extrapyramidal correctors. None of the subjects required hospitalization for psychiatric or organic reasons.

Table 1 shows the mean scores estimated at each of the four assessment times for the three indicators under consideration: BPRS, HDRS and CGI. The contrast tests of the multivariate model and the intra-subject effect have shown statistical significance, as have the mean pairs

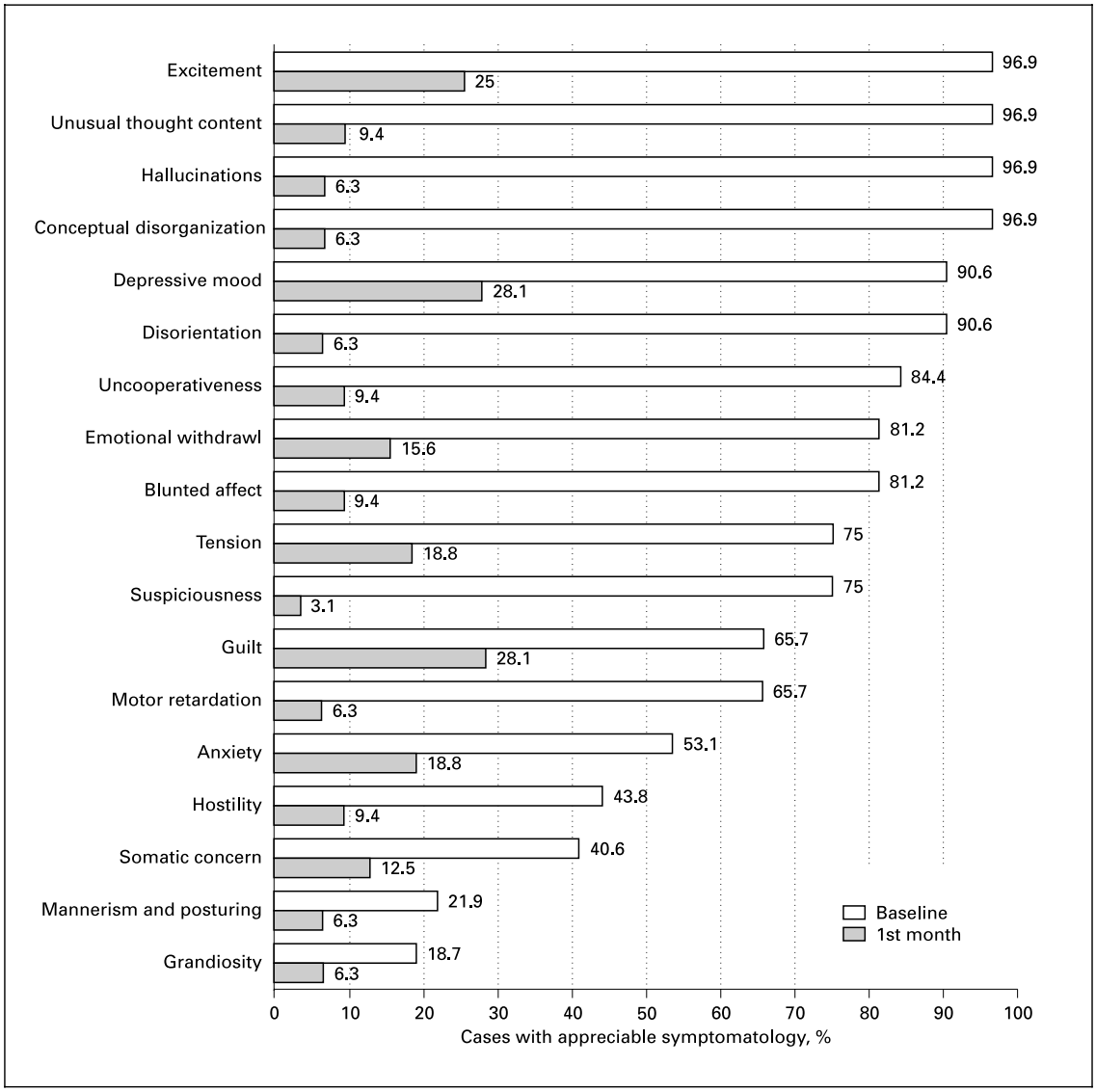

Fig. 1. Evolution (%) of cases with notable symptomatology (values ≥ 2, on a 0 to 4 point range) on the BPRS items.

comparison tests. A significantreduction in symptoms was observed in all cases.

With respect to BPRS, the score obtained in the baseline assessment was 33.1, indicating the presence of a severe psychotic disorder (cutoff value 21). The most outstanding symptoms were: hallucinations (mean = 2.41, SD = 0.6); conceptual disorganization (mean = 2.41, SD = 0.6); unusual thought contents (mean = 2.39, SD = 0.4); depressive mood (mean = 2.31, SD = 0.6); disorientation (mean = 2.22, SD = 0.6); excitement (mean = 2.10, SD = 0.4), and blunted affect (mean = 2.00, SD = 0.6). All of the BPRS symptoms are manifested, albeit mildly (score ≥ 1), in 100% of the sample, except for mannerism and posturing (not present in 4 cases) and grandiosity (not manifested in 3 cases). With respect to the intensity of the psychotic symptoms manifested at onset, this fell by 49.5% at the 1-month assessment, by 71.1% after 3 months, and 84.9% after 6 months. The percentages of changes equivalent to those observed in BPRS were encountered in the HDRS (45.6, 70.6 and 85.3%) and for the CGI (49.3, 81 and 94.1%).

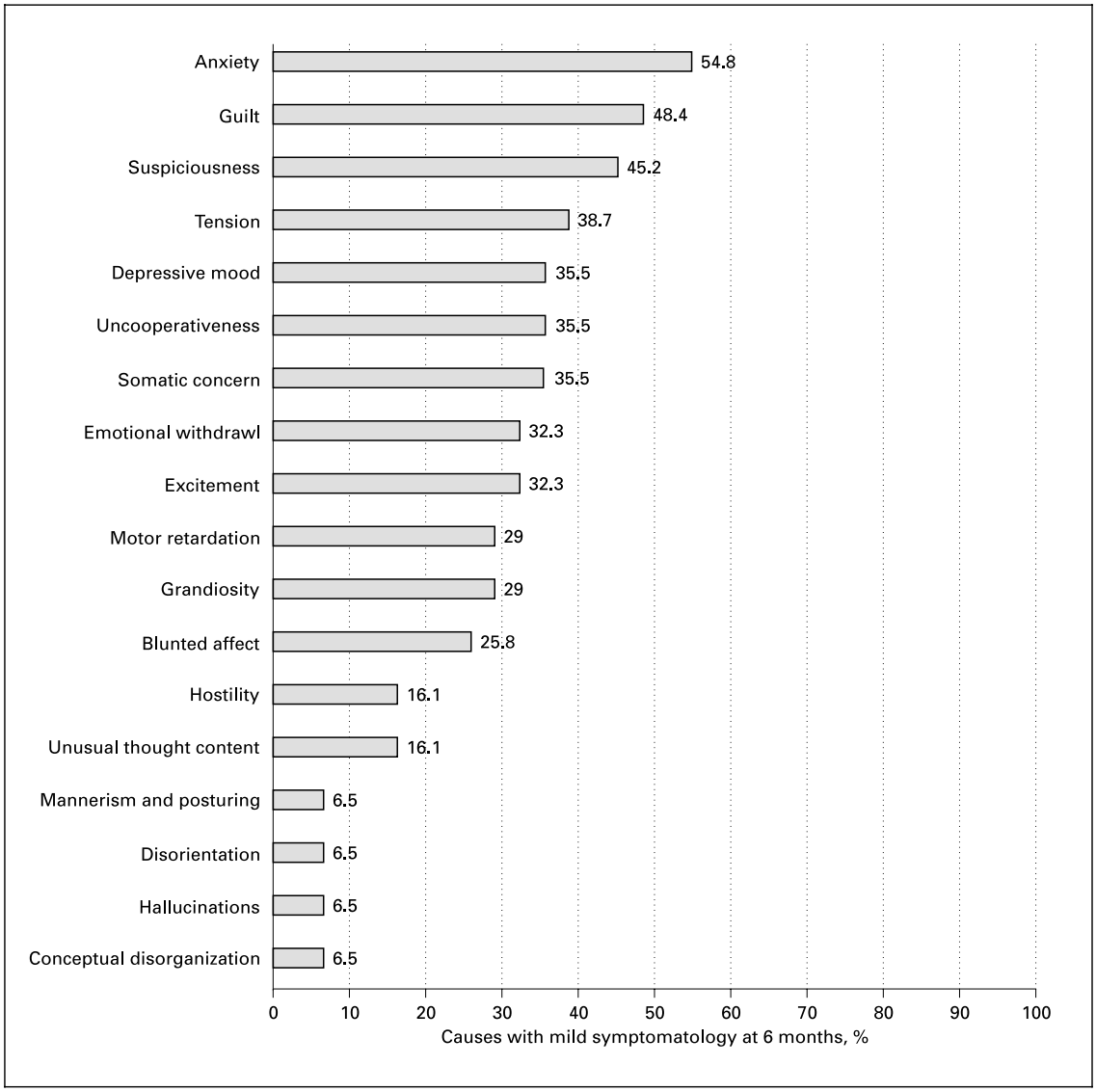

Fig. 2. Percentage of cases with mild symptomatology (values = 1, on a 0 to 4 point range) on the BPRS items after 6 months of treatment.

Figure 1 depicts the evolution of the subjects who presented evident symptomatic intensity (score ≥ 2) in each of the items of the BPRS. The baseline assessment indicated a high incidence of symptoms. In over 75% of cases, 11 of the 18 symptoms of the BPRS were present, with excitement, hallucinations, unusual thought contents, conceptual disorganization, depressive mood and disorientation as the symptoms appearing in over 90% of the cases. The symptoms least often expressed were hostility (43.8%), somatic concerns (40.6%), mannerism and posturing (21.9%) and grandiosity (18.7%). At the 1-month assessment, the symptomatic expression profile was considerably changed. While the initial profile was characterized by a high degree of symptomatic expression with a mixture of positive and negative symptoms, with priority for the former, the 1-month assessment indicated a greater proportion of cases with negative affect manifestations: guilt (28.1%); depressive mood (28.1%); excitement (25%); tension (18.8%), and anxiety (18.8%). The proportion of cases with moderate or severe positive symptoms was considerably reduced at the 1-month assessment: unusual thought contents (9.4%), and hallucinations

(6.3%). The 3-month assessment only recorded scores of more than 2 points for three symptoms (guilt, hostility and suspiciousness), which were manifested by 1 subject. In no case were scores of more than 2 encountered for any of the 18 symptoms in the 6-month assessment, but mild/doubtful manifestations (score 1) were observed, as shown in figure 2.

Discussion

In this article, we present one of the largest samples of patients with psychotic symptoms induced by the consumption of ecstasy published to date, due to the day-to-day work in situ by 2 public health professionals as part of a wide-ranging program for the prevention and detection of drug consumption in local neighborhoods. Their good efforts have made it possible to gain the confidence of these consumers and created opportunities for the early diagnosis and treatment of these disorders. In our opinion, combining the efforts of primary and secondary prevention resources represents an interesting strategy to cope with the possible problems associated with the use/abuse of substances such as meta-amphetamine, especially when these are more frequent in clinical situations and we are somewhat short on specific resources for this type of addiction.

With respect to the presentation of the ecstasy-induced psychotic disorder, the data point to a severe symptomatic syndrome at baseline, when the subjects first come to the health care services. The mean scores on the BPRS and HDRS are above the cutoff points defining a severe degree of pathology, and the assessment effected by the clinician (GCI) is also one of moderate severity. The symptoms most often emerging are positive (delusions and hallucinations), as is typical in the diagnosis of this type of disorder, as well as disorientation, excitement and conceptual disorganization. But there were also considerable negative symptoms, particularly with regard to signs of depression (depressive mood, guilt and blunted affect). The intensity with which the syndrome presents undoubtedly makes it necessary to have a speedy intervention from the clinical and pharmacological standpoint.

In the clinical handling of addictions, we have been somewhat hamstrung in terms of first-choice neuroleptics for the induced psychotic syndromes, in comparison with the relative success described in other studies with typical neuroleptic drugs [4–13]. With the arrival of the atypical neuroleptics and their lukewarm introduction to psychiatric pathologies associated with the consumption of drugs, descriptions began to be published on the effectiveness of this neuroleptic medication [42, 43]. These induced syndromes are characterized by the presence of hallucinations or delusional ideas after the consumption of substances, with the onset and progression of psychiatric manifestations other than primary psychotic disorder, symptoms well known with the use of amphetamines and cocaine [44]. In our trial, the use of olanzapine has been shown to be effective in view of the relevant reduction in symptoms right from the first month and maintained until the end of the study period. We believe that these results may have to do with the efficacy of olanzapine with regard to positive and negative symptoms, as well as the associated depressive symptoms [45].

In all of the assessment instruments used in this study, a significant reduction in symptoms has been detected at both the statistical and clinical levels. The psychiatric (BPRS) and depressive (HDRS) severity already went in the first month from severe to moderate; by the third month subjects continued to present moderate psychiatric symptoms, but the severity of depression dropped considerably. Finally, symptoms ceased to be clinically relevant by the sixth month of treatment, although a certain residual syndrome remained characterized by mild symptoms of anxiety and depression. On the other hand, it is worth highlighting the scant adverse effects described by the patients and the high retention rate encountered (96.9% of cases remained in treatment until the 6 months were up).

Although the results presented may seem to be illuminating with regard to the symptomatic description of ecstasy-induced psychotic disorder and the therapeutic results of olanzapine, we feel that these results need to be considered with some caution. The trial's characteristics (observational design), the lack of a control group, the absence of biological testing and the determination of substance use, and the possible interference of uncontrolled variables are sufficient reasons for considering the existence of constraints to this trial. When it comes to considering the validity of the findings, it is an important advantage to use controlled designs with the inclusion of untreated groups or alternative treatment control groups [46]. The use of an untreated control group would allow verification with greater certainty of whether, for instance, the fast reduction in symptoms over the first month is due to a spontaneous reduction following the conclusion of the intoxication by the substance or due to the effects of its withdrawal syndrome, or whether this improvement is an effect of the neuroleptic treatment. Nonetheless, the possibility of using an untreated control

group was considered ethically questionable in view of the severity with which the syndrome presented. The approach proposed by our group for future trials is based on the use of control groups receiving typical and atypical antipsychotic drugs and the possibility of using antidepressive medication. Furthermore, and with a view to distinguishing the symptomatic expression of substance-induced psychotic disorders and so lead to a differential diagnosis, we feel that its comparison with other psychotic disorders, especially first onset disorders, is necessary.

On the other hand, it would also be appropriate to use biological determinations in order to reinforce the assessment of symptoms using scales. In our trial, no substance detection tests were employed, in the perhaps excessive confidence that the statements of the patients themselves with regard to their consumption were reliable. The follow-up and determination of the use of ecstasy and other substances will allow us, initially, to make a differential diagnosis with respect to the type of substance-induced psychotic disorder and, secondly, to assess the impact that the use of such substances might have on the evolution of the syndrome.

Conclusions

Initially, ecstasy-induced psychotic disorders present a severe clinical syndrome characterized by the presence of both positive and negative symptoms and a large number of signs of depression. The use of olanzapine is seen to be the drug of choice with regard to the absence of side effects and the evident remission of symptoms already in the first month. Nonetheless, additional controlled studies are required in order to verify the results obtained in this trial with a greater degree of validity.

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