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# Acute treatment of Cycloid Psychosis: Study on a sample of naive hospitalized patients with First-Episode Psychosis (FEP)

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**Introduction.** In spite of the historic, clinical and therapeutic importance of cycloid psychosis, no controlled studies have been performed as yet on its treatment. Electroconvulsive therapy has classically been the treatment of choice and the first generation antipsychotics have not been indicated. This study has aimed to analyze the acute treatment (and response to it) of cycloid psychoses.

**Methodology.** In a sample of 75 hospitalized medication-naïve patients treated for a First Psychotic Episode (FPE), possible cases of cycloid psychoses were detected using the Perris and Brockington operative diagnostic criteria. The sample was divided into "cycloids" and "non-cycloids" and both groups were compared based on clinical and therapeutic variables.

**Results.** All the patients were treated with second generation antipsychotics. No significant differences ( $p=0.17$ ;  $t=1.39$ ) were found in the antipsychotic dose prescribed (equivalents of chlorpromazine). However, significant differences were observed in the improvement on hospital discharge (clinical global impression severity: CGI-S), with better response in the "cycloid" group ( $p=0.002$ ;  $u=162$ ). Significant differences were also observed in the dose of benzodiazepines, there being significantly greater improvement for the "cycloid" group ( $p>0.001$ ;  $u=28$ ).

**Conclusions.** Without contradicting the classical idea of the treatment of cycloid psychoses, the present study contributes to the opening of a new therapeutic prospect. Thus, the use of second generation antipsychotics could have a particularly beneficial effect, especially if combined

with high doses of benzodiazepines in the acute treatment of cycloid psychoses. However, controlled studies need to be carried out to confirm this.

**Keywords:** Cycloid Psychosis, Treatment, First Episode Psychosis, Antipsychotics

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## Tratamiento de la Psicosis Cicloide en fase aguda: Estudio sobre una muestra de pacientes libres de medicación hospitalizados por un Primer Episodio Psicótico (PEP)

**Introducción.** A pesar de la relevancia histórica, clínica y terapéutica de las psicosis cicloides, hasta el momento actual no se han realizado estudios controlados sobre su tratamiento. La terapia electroconvulsiva ha sido clásicamente de elección y los antipsicóticos de primera generación no han estado indicados. El presente estudio tiene como objetivo analizar el tratamiento agudo (y la respuesta al mismo) de las psicosis cicloides.

**Metodología.** En una muestra de 75 pacientes libres de medicación hospitalizados y tratados por presentar un Primer Episodio Psicótico (PEP), se detectaron los posibles casos de psicosis cicloides utilizando los criterios diagnósticos operativos de Perris y Brockington. Se dividió la muestra en "cicloides" y "no cicloides" y se compararon ambos grupos en función de variables clínicas y terapéuticas.

**Resultados.** Todos los pacientes fueron tratados con antipsicóticos de segunda generación. No se encontraron diferencias significativas ( $p=0.17$ ;  $t=1.39$ ) en la dosis de antipsicótico pautado (equivalentes de clorpromacina), pero si se observaron diferencias significativas en la mejoría al alta hospitalaria (CGI-S), con una mejor respuesta en el grupo de los "cicloides" ( $p=0.002$ ;  $u=162$ ). También se observaron

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diferencias significativas en la dosis de benzodiacepinas, siendo notablemente mayor para el grupo de "cicloides" ( $p>0,001$ ;  $u=28$ ).

**Conclusiones.** Sin contradecir la idea clásica del tratamiento de las psicosis cicloides, el presente estudio contribuye a abrir una nueva expectativa terapéutica. De manera que en el tratamiento agudo de las psicosis cicloides, el uso de antipsicóticos de segunda generación podría tener un efecto particularmente beneficioso, especialmente si se combina con benzodiacepinas a dosis altas. Si bien es preciso la realización de estudios controlados que confirmen este dato.

**Palabras clave:** Psicosis Cicloide, Tratamiento, Psicosis, Primer Episodio Psicótico, Antipsicóticos

## INTRODUCTION

The concept of cycloid psychosis, initially described by Leonhard<sup>1</sup> has a long tradition in European psychiatry.<sup>2,3</sup> However, the clinical characteristics of cycloid psychoses have been described by other authors and/or schools, with many names such as: acute schizoaffective psychosis,<sup>4</sup> schizophreniform psychosis,<sup>5</sup> reactive psychosis,<sup>6</sup> atypical psychoses (also called Mitsuda psychosis),<sup>7</sup> puerperal psychosis,<sup>8</sup> bouffée délirante.<sup>9</sup> These different names for possibly the same disorder are manifestations of the emphasis placed on its different characteristics. Finally, the concept of cycloid psychosis has prevailed<sup>10</sup> and there is currently wide consensus among different authors on the principal characteristics of cycloid psychoses: acute psychotic disorders of abrupt onsets, recurrent and benign, whose symptoms are not typically affective or schizophrenic, but rather essentially polymorphic.<sup>11</sup>

In spite of the historic, clinical and therapeutic importance of cycloid psychoses, no controlled studies have been performed as yet on the treatment. The reason is mainly because the nosological systems of consensus (ICD-10<sup>12</sup> and DSM-5<sup>13</sup>) have placed scarce interest in its diagnosis and because of the scant attention traditionally shown in regards to the therapeutic aspects of the transient psychoses.<sup>14</sup> Thus, the data on its treatment are based on the clinical experience in non-controlled studies and on references published on isolated cases.<sup>15,16</sup>

Considering the diagnosis of cycloid psychosis, the treatment must be analyzed from two angles: treatment of the acute episode and maintenance treatment (interphase).

Regarding the treatment of the acute episode, electroconvulsive therapy (ECT) has been the treatment of choice for many years,<sup>17</sup> above all in disorders with significant motor involvement,<sup>18</sup> this producing intense improvement after a few sessions. Both the American literature as well as

the school of Leonhard<sup>1</sup> reported the satisfactory use of ECT in the decrease of the fundamental biological symptoms and in the psychomotricity alterations.

Classically, the use of first generation antipsychotics has not been indicated in the acute treatment of cycloid psychoses. However, currently, there are increasingly more clinicians who name the atypical antipsychotics (second generation) for possible use due to the mood stabilizing properties.<sup>3,17</sup>

Benzodiazepines at high doses have also been used during the acute phase.<sup>17</sup> Several authors stress that some cycloid psychoses tend to remit spontaneously and that it is also possible in some cases to identify and approach the precipitating factors of the episode. Thus, in those cases in which the symptoms are not very disruptive, a conservative treatment (e.g. using benzodiazepines and treating the precipitating factor) could be recommendable.

Another possibility in regards to treatment of the acute phase is the use of antiepileptic drugs (carbamazepine or valproate) in combination with the treatment. And in the case of cycloid psychoses related with low estrogen level, there seems to be slight evidence about the possible beneficial effect of estrogen replacement therapy.<sup>19,20</sup>

The present study has aimed to analyze the acute treatment (and its response) of cycloid psychoses through their detection in a sample of medication naive-patients who have been hospitalized due to a First Psychotic Episode (FPE).

## METHODOLOGY

The present work is an observational study based on a sample of medication-naïve patients who presented a First Psychotic Episode (FPE). A total of 75 patients hospitalized in the acute unit of a general hospital in Madrid (Spain) between 2005 and 2009 who presented a First Psychotic Episode consistent with the diagnostic criteria DSM-IV-TR<sup>21</sup> of schizophreniform disorder, schizoaffective disorder or schizophrenia were included.

Inclusion Criteria for the study were: 1) Patients hospitalized in the acute unit, who presented a First Psychotic Episode (FPE) consistent with the diagnostic criteria DSM-IV-TR<sup>21</sup> of schizophreniform disorder, schizoaffective disorder or schizophrenia; 2) medication-naïve patients with no history of previous treatment with antipsychotics; 3) Ages from 18-65 years; 4) who were capable of giving their informed consent.

Exclusion criteria established were: 1) any of the inclusion criteria were not fulfilled; 2) Medical diagnosis that could produce changes in the white matter (e.g. HIV,

multiple sclerosis); 3) Brain disorder that could cause cognitive deficit or behavior alterations (e.g. history of cranioencephalic trauma, cerebrovascular disease); 4) Unstable medical condition (e.g. diabetes or uncontrolled hypertension); 5) Lifelong history of substance dependence according to DSM-IV-TR criteria.<sup>21</sup>

Each subject was carefully studied, obtaining an adequate clinical history, medical examination and laboratory studies to assure they complied with the inclusion criteria. In addition to the previously mentioned requirements, the patient was offered clear and detailed information on the study characteristics, requirements and consequences. Each and every one of them gave their informed consent, in which they demonstrated they agreed with the study. The patients were included and evaluated at the moment of their admission and after hospital discharge. All were subjected to a complete clinical interview carried out by the same psychiatrist.

Regarding the duration of untreated psychosis (DUP), a definition in accordance with the recommendations of Bromet et al.<sup>22</sup> was used. Using a semistructured interview with the family and the patient, data were collected on the chronology of the first psychotic symptoms. Based on said information, time of evolution was established in days of the psychotic disorder for each case, then calculating age of onset of the patient at the time of the debut of the psychosis.<sup>23</sup>

The detection of the possible cases of cycloid psychosis was performed by applying the Perris and Brockington<sup>24</sup> operative criteria for the diagnosis of cycloid psychosis (1982), which continues to be the used most at present.<sup>15,16</sup> Furthermore, on the contrary to the initial diagnostic criteria described by Leonhard, those of Perris and Brockington do not include the good prognosis criterion (typical characteristic of the cycloid psychosis) in the definition, which avoids a tautological definition of the disorder in regards to its evolution.<sup>16</sup> These criteria are the following: 1) Acute psychosis not related with drug consumption and without any organic basis, which appears for the first time between 15-50 years of age. 2) Sudden appearance with rapid progression towards psychosis. 3) Presence of at least four of the following inclusion criteria: confusion, incongruent mood, delusional ideas of any type, hallucinations of any type, overwhelming anxiety (psychotic anxiety), deep feelings of happiness or ecstasy, kinetic or hyperkinetic type motility alterations, special interest in death and discreet mood changes. 4) There is no specific combination, but rather the symptoms can change quite frequently, showing a bipolar character. After, the sample was divided into two groups, that is "cycloid" and "non-cycloid," based on whether the diagnostic criteria of cycloid psychosis were fulfilled or not, respectively.

The severity of the psychotic episode was evaluated with the clinical global impression severity (CGI-S) subscale,

a descriptive scale that provides qualitative information on the severity of the picture. To evaluate the psychotic symptoms, the Positive and Negative Syndrome Scale (PANSS) was applied.

At the time of hospital discharge, the treatment prescribed for each one of the patients of the sample was recorded. The dose on hospital discharge was transformed into equivalents of chlorpromazine, according to the recommendations of Woods<sup>25</sup> for the patients who received antipsychotic medication. Regarding the use of benzodiazepines, when the patient was described any of them on hospital discharge, the dose was transformed into equivalents of clorazepate dipotassium.<sup>26</sup> Duration of hospital time, measured in days, was also evaluated on discharge.

Improvement at the time of hospital discharge was evaluated using the CGI Improvement subscale, a descriptive scale that evaluates the improvement experienced by the patients in regards to his/her baseline status, independently of whether it is totally due to the treatment.

Qualitative variables were expressed by means of their distribution of frequencies and the quantitative variables by their mean  $\pm$  standard deviation (SD). The continuous variables not normally distributed were expressed in the median and interquartile range (IQR, 25-75). For comparison between groups of quantitative variables, the Student's T test or Mann-Whitney U non-parametric test was used. In the case of qualitative variables, comparison between groups was evaluated using the chi-square test or Fisher's exact test (if more than 25% of the expected values were less than 5). Significance level accepted for all these tests was 5%. The data processing and analysis was performed using the SPSS statistical program version 15.0 for Windows (SPSS, Chicago, IL, USA).

## RESULTS

It was observed that a total of 11 patients (14.7%) fulfilled the diagnostic criteria for cycloid psychosis versus 64 (85.3%) patients who did not fulfill them.

Average age of onset of all the patients was 27.6 years ( $SD \pm 6.30$ ). No significant differences were found in onset age ( $p=0.112$ ,  $t=-1.607$ ) between the "cycloid" psychoses group and those of the "non-cycloid" psychoses. Mean age of onset for the "cycloid" group was 30.4 years ( $SD \pm 8.5$ ) and the "non-cycloid" group 27.1 years ( $SD \pm 5.6$ ) (Table 1).

For all the sample, median duration of the duration of untreated psychosis (DUP) was 60 days, with an interquartile range of 15 to 120 days. Significant differences were found between both groups ( $p<0.001$ ;  $u=53$ ), with a shorter duration in the "cycloid" group (Table 1).

**Table 1** Differences between "cycloids" and "non-cycloids"

	"cycloids"	"non-cycloids"	significance level		
	n=11	n=64	t	U	p
Age (years): Mean $\pm$ SD	30.4 $\pm$ 8.5	27.1 $\pm$ 5.6	-1.607		0.112
DUP (days): Median (IQR)	7 (4-7)	90 (90-150)		53	0.000
CGI-Severity: Median (IQR)	5 (5-6)	5 (4-5)		234	0.059
Total PANSS: Mean $\pm$ SD	110.5 $\pm$ 22.1	87.5 $\pm$ 22.8	-3.107		0.003
APS dose (mg): Mean $\pm$ SD	392.3 $\pm$ 206.1	327.2 $\pm$ 130.2	-1.385		0.170
BZD dose (mg): Median (IQR)	45 (30-100)	0 (0-10)		28	0.000
Duration of hospitalization (days): Mean $\pm$ SD	23 $\pm$ 12.3	21.1 $\pm$ 12.3	-0.443		0.659
CGI-Improvement: Median (IQR)	1 (1-1)	2 (1-2)		162	0.002
	Count (%)	Count (%)		X <sup>2</sup>	p
Gender				3.5	0.060
-Woman	8 (72.7)	27 (42.2)			
-Man	3 (27.3)	37 (57.8)			

DUP: Duration of untreated psychosis  
 APS: Antipsychotics (Chlorpromazine equivalence)  
 BZD: Benzodiazepine (clorazepate dipotassium equivalence)  
 CGI: Clinical Global Impression  
 PANSS: Positive and Negative Syndrome Scale for Schizophrenia  
 IQR: interquartile range

Regarding gender, 53.3% (n=40) of the sample were men while 46.7% (n=35) were women. There were also no significant differences between both groups ("cycloid" and "non-cycloid") ( $p=0.06$ ,  $\chi^2=3.5$ ) (Table 1).

In the CGI-Severity, differences were found (although not statistically significant ones) ( $p=0.06$ ;  $u=234$ ) between the "cycloids" and "non-cycloids." The same median score was observed for both groups (CGI-Severity=5= "Markedly ill"), however there was a greater range in the "cycloids" than in the "non-cycloids" (IQR 5-6 and IQR 4-5, respectively) (Table 1).

Regarding the clinical measurements of the psychotic symptoms, significant differences were found in the total PANSS score ( $p=0.003$ ;  $t=-3.107$ ) when comparing both groups. The total score was greater in the "cycloid" group" (110.5 $\pm$ 22.1) than in the "non-cycloid" (87.5 $\pm$ 22.8) (Table 1).

All the patients had been treated with second generation atypical antipsychotics (risperidone, ziprasidone, olanzapine, aripiprazole or quetiapine) in single drug antipsychotic therapy (Table 2). Median dose of antipsychotics prescribed on hospital discharge and transformed into equivalents of chlorpromazine was 337.3 milligrams (SD $\pm$ 144) for the entire sample. No statistically significant differences were found between both groups ("cycloids" and "non-cycloids"

in antipsychotic dose (equivalents of chlorpromazine) administered on hospital discharge ( $p=0.17$ ;  $t=-1.385$ ) (Table 1).

The benzodiazepine dose prescribed on hospital discharge and transformed into equivalents of clorazepate dipotassium was 0 milligrams IQR (0-22.5), since only 41.3% (n=31) of the patients were prescribed benzodiazepinic treatment on discharge versus 58.7% (n=44) of those who were not prescribed this treatment. Although it was observed that 100% of the "cycloid" patients were prescribed benzodiazepines on discharge, only 31.3% of the "non-cycloid" patients required this treatment. Significant differences ( $p<0.001$ ;  $u=28.0$ ) were also found in the benzodiazepine dose (in equivalents of clorazepate dipotassium) between both groups (Table 1).

ECT (Electroconvulsive treatment) was not administered to any of the patients in the sample and they had not been prescribed any anti-seizure or antidepressant treatment.

The number of hospitalization days for the total sample was 21.5 days (SD $\pm$ 12.4). There were no significant differences in the number of hospital days between the "cycloid" and "non-cycloid" group ( $p=0.659$ ;  $t=-0.443$ ) (Table 1).

**Table 2** Antipsychotic treatment prescribed

	"non-cycloids" n=64	"cycloids" n=11	TOTAL OF THE SAMPLE n=75
Patients treated with Risperidone	35	6	45
Dose (mg): Mean $\pm$ SD	5.5 $\pm$ 2.2	6.2 $\pm$ 3.4	5.7 $\pm$ 2.2
Patients treated with Olanzapine	8	2	10
Dose (mg): Mean $\pm$ SD	23 $\pm$ 7	35 $\pm$ 7	25.4 $\pm$ 8.2
Patients treated with Ziprasidone	14	2	16
Dose (mg): Mean $\pm$ SD	182.9 $\pm$ 66	200 $\pm$ 56.4	185 $\pm$ 63.5
Patients treated with Aripiprazole	6		6
Dose (mg): Mean $\pm$ SD	17 $\pm$ 7.6		17 $\pm$ 7.6
Patients treated with Quetiapine	1	1	2
Dose (mg): Mean $\pm$ SD	600	600	600

Significant differences were found in the CGI Improvement Scale ( $p=0.002$ ;  $u=162$ ) between "cycloids" and "non-cycloids," with a significantly greater improvement in the "cycloids" (Table 1).

## DISCUSSION

Detection of the possible cases of cycloid psychosis made it possible to observe that these syndromes accounted for 14.7% of all the admissions for a first psychotic episode, which agrees with the few previous studies that state this figure as between 10–15%.<sup>15</sup>

As is logical, the DUP (duration of untreated psychosis) in "cycloid" patients was much less than the rest of the first "non-cycloid" episodes since the diagnostic criteria of Perris and were used, which include, among others "sudden onset: several hours to several days pass from the normal state until the peak of the psychosis."

Another differential findings of cycloid psychoses regarding the rest of first psychotic episodes was the clinical impression of greater severity and higher score on the PANSS-total observed in the "cycloid" patients. This would be explained by the psychopathological addition of the confusional symptoms (excited and/or inhibited) and motility alterations (hypo and/or hyperkinetics) that characterize cycloid psychoses.

Regarding the treatment regime on hospital discharge, the first thing that comes to mind is the antipsychotic dose. Although it was apparently higher for the "cycloid" group, it was not statistically different from the dose prescribed for the "non-cycloid" group. These results would contrast with the classical idea according to which antipsychotics, at least the first generation ones, would not be indicated for acute treatment of cycloid psychoses. This is even truer when the

response to the treatment was favorable in all the "cycloid" patients.

However, it should be remembered that:

1. Up to now, no controlled studies have been conducted on the treatment of cycloid psychoses.
2. The data on treatment are based on clinical experience, on non-controlled studies and on references published on isolated cases.
3. The classical idea that antipsychotics are not indicated in the treatment of cycloid psychoses basically refers to the first generation antipsychotics. This is because in the akinetic states, the typical antipsychotics could facilitate the development of complications such as the appearance of a malignant neuroleptic syndrome and/or lethal catatonia.<sup>3,17</sup>
4. In the sample of the current study, all the "cycloid" patients had been treated with second generation atypical antipsychotics. Currently, recent studies<sup>3,14,27</sup> name the atypical antipsychotics as a possibility for use due to their mood stabilizing properties.

On the other hand, on the contrary to the findings on treatment with antipsychotics, when the benzodiazepine dose on discharge were compared between the "cycloid" and "non-cycloid" group, it was this dose was found to be substantially greater on discharge in the "cycloid" group. In this sense, benzodiazepines at high doses have classically been used during the acute phase of cycloid psychoses, possibly because of the catatoniform component (in which benzodiazepines are the treatment of choice).

It should be remembered that in the words of Leonhard,<sup>1</sup> "cycloid psychoses are a group of acute and self-limiting psychotic disorders that can be diagnosed reliably based on

the cross-sectional evaluation of the clinical characteristics of the picture." This statement has created some conceptual disorder over the years as it supposes that the notion of "self-limited" and "cross-sectional" is synonymous to will "briefness." In fact, according to Perris,<sup>28</sup> the duration of each one of the cycloid psychosis episodes generally ranges from several weeks to several months, although the duration may be less than one week or up to more than one year in a substantial minority of patients. For this reason, it does not seem strange that differences were not found in the duration in days of the hospital admission between "cycloid" patients and the remaining first psychotic episodes. Replication of this finding, which has already been described similarly by other authors<sup>15</sup> is important and should be taken into consideration by the clinicians in order to avoid an erroneous diagnosis of schizophrenia, above all in patients with first psychotic episode.

Finally, as previously mentioned cycloid psychosis patients totally recover from the psychotic episode. And in spite of the good response to treatment and improvement found in general with first psychotic episodes, the results of the current study regarding improvement on hospital discharge are easily predictable. That is, it seems logical and to be expected that "cycloid" patients would score significantly better than the rest of the first psychotic episodes on the subscale of CGI Improvement.

## CONCLUSIONS

Regarding acute treatment of cycloid psychoses, this could be summarized as follows:

1. Treatment with antipsychotic or benzodiazepines and mood stabilizing or electroconvulsive treatment is purely empirical and experience-based.
2. There are no randomized comparative studies between the different interventions or compared to placebo.
3. There are no definitive conclusions on the logarithms developed with atypical antipsychotics or combinations. However their use undoubtedly opens a new therapeutic expectation.

The current study, without contradicting the classical idea of acute treatment for cycloid psychoses contributes to opening a new therapeutic expectation. Thus, in the treatment of the first episode of a cycloid psychosis, the use of a typical antipsychotics could have an especially beneficial effect, particularly if combined with high doses of benzodiazepines. In the case of atypical (or new generation) antipsychotics, they could be postulated as a potential therapeutic tool thanks to their effect on the affective modulation through the affinity for 5HT (5HT<sub>2A</sub>, 5HT<sub>1A</sub>, 5HT<sub>2C</sub> receptors and more recently described 5HT<sub>7</sub>), while

the use of benzodiazepines associated to high doses would be supported by the hypothesis that an additional use of anxiolytic substances may often improve the symptoms of severe anxiety that characterizes cycloid psychoses.

However, the present study has some limitations, the most important being that referring to the small sample size. On the other hand, the greater severity of the psychotic symptoms observed in cycloid psychoses could justify the differences in the treatment chosen. Thus, performance of controlled studies that confirm these data are needed.

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