

# Naturalistic evaluation of inpatient treatment of mania in a private Brazilian psychiatric hospital

## Avaliação naturalística do tratamento da mania em um hospital psiquiátrico particular

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**Abstract Objective:** To describe the clinical practices on the treatment of mania in a Brazilian hospital, and to compare them to other international similar reports and practice guidelines.

**Methods:** Chart revision of 425 consecutive admissions (269 patients) for the treatment of manic or mixed episodes (ICD-10 criteria) in a private psychiatric hospital of Belo Horizonte, Brazil, from 1996 to 2000. The rates of utilization of each antimanic medication and ECT were compared to those reported in similar international observational studies ( $X^2$ , bicaudate,  $\alpha = 0.05$ ).

**Results:** The observed frequencies of use of each treatment modality were: lithium (71.5%); carbamazepine (34.8%); valproate (9.4%); antipsychotics (83.3%); benzodiazepines (62.4%); antidepressants (7.5%) and ECT (33.2%). The differences detected between local practice and international guidelines were: lower rate of valproate and higher rate of carbamazepine prescription; the use of sine wave devices for ECT; frequent concomitant use of ECT with lithium (72.3%), benzodiazepines (46.8%) and/or carbamazepine (31.2%).

**Conclusions:** These results suggest the need to develop national practice guidelines for the treatment of mania and for the use of ECT, and to promote their propagation through specific medical educational programs, aiming at the standardization of practices based on the available scientific evidence.

**Keywords** Mania. Bipolar disorder. Inpatient treatment. Brazil.

**Resumo Objetivo:** Descrever as práticas clínicas no tratamento da mania em um hospital brasileiro e compará-las com aquelas descritas e recomendadas nas publicações internacionais.

**Métodos:** Revisão dos prontuários de 425 internações consecutivas (269 pacientes) para episódios maníacos ou mistos (CID-10) em um hospital psiquiátrico privado de Belo Horizonte (MG), de 1996 a 2000. As frequências de utilização dos diversos medicamentos e de ECT foram comparadas com as descritas em estudos observacionais estrangeiros ( $X^2$ , bicaudado,  $\alpha = 0,05$ ).

**Resultados:** As frequências observadas de uso de cada tratamento foram: lítio (71,5%); carbamazepina (34,8%); valproato (9,4%); antipsicóticos (83,3%); benzodiazepínicos (62,4%); antidepressivos (7,5%) e ECT (33,2%). As divergências encontradas entre as práticas no tratamento da mania observadas neste estudo e aquelas descritas e recomendadas pelas publicações e diretrizes internacionais foram: o uso menos freqüente de valproato e mais freqüente de carbamazepina; o uso de aparelho de ondas sinusoidais para a ECT; e o elevado uso concomitante de ECT com lítio (72,3%), anticonvulsivantes (31,2%) e/ou benzodiazepínicos (46,8%).

**Conclusões:** Estes achados sugerem a necessidade do desenvolvimento de diretrizes nacionais para o tratamento da mania e uso de ECT e de sua divulgação em programas específicos de educação médica, de forma a uniformizar as condutas fundamentadas na evidência científica disponível.

**Descritores** Mania. Transtorno bipolar. Tratamento em internados. Brasil.

## Introduction

With the increasing worldwide interest in bipolar mood disorder, treatment of manic episodes has shown remarkable development. Chlorpromazine, the first specific antipsychotic drug, was used in a manic patient in 1951, and became the first choice treatment for acute mania<sup>1</sup> before the use of mood stabilizers was implemented. By the end of the 60's, Haloperidol had shown similar efficacy and less sedative and hypotensive effects.<sup>1</sup> Lithium, whose psychoactive effects were initially investigated by John Cade since 1949, was incorporated into clinical practice as a mood stabilizer for bipolar patients by Mogens Schou.<sup>1</sup> Ten years later it became the most used antimanic agent and until now is the most studied one. By the middle of the 60's, anticonvulsants started being tested in treating bipolar disorder.<sup>2</sup> Currently, valproate and carbamazepine<sup>2,3</sup> are important therapeutic alternatives for mania. Before the development of these specific drugs, electroconvulsive therapy (ECT) was the treatment of choice for mania, due to its remarkable efficacy,<sup>4</sup> safety<sup>5</sup> and rapid onset of action.<sup>6</sup> It is currently recommended in resistant manic cases or in situations in which speed of action is required because of extreme agitation or life threatening situations.<sup>6,7</sup> Manic episodes often demand hospitalization to promote safer<sup>1</sup> and faster<sup>8</sup> responses to treatment.

There are no recent publications describing treatments for manic episodes in Brazil and Latin American publications on ECT are extremely reduced in number and have only scarce quantitative data. This lack of information brings difficulties for mental health planning and determination of costs. Since the specificities of Brazilian psychiatric practice are not taken into account, establishing the appropriate educational strategies in psychiatry based on foreign data is problematic. This study intends to present the first specific description of clinical practices for inpatient treatment of mania in a Brazilian institution, comparing them with those described in international publications and recommended by therapeutic guidelines and consensus.

## Methods

This is a retrospective observational study, comprising both descriptive and comparative elements. It was performed in a private psychiatric hospital situated in the southern part of Belo Horizonte, the capital of the state of Minas Gerais and has been approved by the institution's Commission of Medical Ethics. The hospital has 136 beds (55 in the women's ward and 81 in the men's ward) for private and HMO patients coming from the city and adjacent regions, prioritizing admissions of acute cases. ECT has been used in this institution for more than 50 years, and it is one of the few local clinics where this treatment is currently offered.

## Sampling

We reviewed the charts of all consecutive admissions between January 1, 1996, and December 31, 2000, in which discharge diagnosis was one of the following International Classification of Diseases, 10<sup>th</sup> edition (ICD-10) categories (or ICD-9 equivalent): manic episode (F30.1, F30.2, F30.9); bipolar disorder, manic episode (F31.1, F31.2); bipolar disorder, mixed

episode (F31.6); bipolar disorder, not otherwise specified (F31.9); psychosis non-organic, not otherwise specified (F29). Criteria for manic or mixed episode had to be met in at least one admission during that period. Out of the 533 patients whose charts were reviewed, 269 met those criteria. The reasons for excluding the other 264 patients were: a) the chart did not contain enough information to ascertain diagnosis; or b) other diagnosis, previously incorrectly coded as mania; or c) bipolars without admissions for manic or mixed episode within the 5-year period of the study; or d) other psychotic disorders, coded as F29. If the patient was hospitalized more than once for manic or mixed episode on that 5-year period, all hospitalizations were included, comprising a total of 425 admissions.

## Definitions

*Psychotic features* were the presence of delusions, hallucinations, or loosening of associations (but not flight of ideas). *Suicidality* included desire of dying, suicidal ideas, gestures or attempts at the current episode. *Violent behavior* was the presence of verbal hostility or physical aggression towards objects or against others. The variable *cardiovascular disease* encompassed a concurrent diagnosis of either arterial hypertension or of any other cardiac disorder, even if the condition was stable. *Marital status* was simplified into married and not married. Some other variables pertaining psychiatric history (previous ECT, number of previous episodes, and previous treatment response) could have influenced treatment choice but were not available for a sufficient number of patients and could not be explored.

Since the design of this study is retrospective and naturalistic, treatment was allocated at the discretion of each psychiatrist. ECT was not an exclusive treatment and most patients received concomitant psychiatric medication.

Inpatients who received neuroleptics in average doses equivalent to at least 300 mg/day of Chlorpromazine, or any atypical antipsychotic drug, were considered to be in use of *antipsychotic drugs*. Lithium, Carbamazepine and Valproate were medications considered to be *mood stabilizers*. Responses to treatments were not assessed in this study.

## Statistical analysis

In descriptive statistics, we computed means for variables following gaussian distribution and medians for non-gaussian variables, along with their respective 95% confidence intervals.

In order to contrast the frequency of use of each treatment strategy among the patients in this study and that reported in foreign studies, the chi-square method was used, with a statistical significance of 95% ( $p < .05$ , bicaudate). For these analyses, comparisons were made between our data and the frequency of use of each treatment observed in the pooled data reported in other observational studies.

## Results

### Sample description

Table 1 comprises the demographic and clinical features of these patients. The sample was composed by 47.5% male and

**Table 1 - Demographics and clinical features of 425 admissions of manic patients in a psychiatric hospital of Belo Horizonte, 1996 to 2000.**

Features	N	%
Males	202	47.5
Females	223	52.5
Married	172	40.7
Had previous Hospitalizations*	318	89.6
Mixed states	32	7.5
Substance abuse	41	9.7
Cardiovascular disease	84	19.8
Thyroid disease	26	6.1
Suicidality	48	11.3
Psychotic features	215	50.6
Violent behavior	210	49.4

\*Available data in 355 observations.

**Table 2 - Treatment strategies in 425 hospitalizations of manic patients in a psychiatric hospital of Belo Horizonte, 1996 to 2000.**

Treatments	N	%
Mood stabilizers:	382	89.9
Only lithium	197	46.4
Only Carbamazepine	62	14.6
Only valproate	16	3.8
lithium + carbamazepine	83	19.5
lithium + valproate	21	4.9
lithium + carbamazepine + valproate	3	0.7
Antipsychotics	354	83.3
Benzodiazepines	265	62.4
Antidepressants	32	7.5
ECT	141	33.2

52% female admissions. The mean age, considering all admissions, was 42.0+/-12.6 years (ranging from 13 to 79 years).

### Treatment strategies

Table 2 displays the frequency of each type of treatment given to inpatients in this sample during their hospitalizations. All patients received some kind of psychiatric medication during their stay, either as monotherapy or in combination with other treatments. In 382 admissions (89.9%), patients received at least one mood stabilizer (lithium, carbamazepine and/or valproate). Antipsychotics were used in 354 admissions (83.3%). In 27 admissions (6.4%), patients were not given mood stabilizers or ECT, although they all received an antipsychotic drug. The most frequent drug combination was lithium plus antipsychotics (n=253; 59.5%). Benzodiazepines were used in 265 admissions

(62.4%) and antidepressants in 32 (7.5%), 15 of which were for mixed episodes.

In 141 admissions (33.2%) ECT was administered using a sine wave device. The position of electrodes was not specified in the charts. The frequency of ECT sessions was three per week in most of the cases (83%). Energy settings and the length of convulsions were also not recorded. All patients treated with ECT received concomitant psychiatric drugs daily. Table 3 lists the medications used in association with ECT: lithium was used in 102 cases (72.3% of those who received ECT), carbamazepine in 49 cases (34.8%) and valproate in 7 cases (5%).

A median of six sessions by course of ECT was observed. (Confidence Interval 95% (CI) =5.0; 6.0). This number is smaller than the 6.6 sessions per course reported by Malla;<sup>10</sup> the 8 described by Alexander et al;<sup>11</sup> the 13.3 as used by Strömngren<sup>12</sup> and the 8.8 reported by Black et al.<sup>13</sup> Abrams<sup>5</sup> postulates that 8 to 12 applications are ideal for the treatment of manic episodes, which is also higher than that reported in our study. On the other hand, the number of sessions per course of ECT that we reported is within the interval of 5.4 to 11 sessions per course described in a thorough review on 50 years of the use of ECT in mania, by Mukherjee et al.<sup>4</sup> It is also within the limits of 6 to 12 applications suggested — though not specifically for mania — by the American Psychiatric Association (APA) and the National Institute of Mental Health.<sup>7</sup>

Regarding anesthesia for ECT, all patients were previously pre-medicated with succinylcholine and thionembutal. Nowadays the APA recommends the use of methohexital as an an-

**Table 3 - Medications used in combination with ECT (n=141) in hospitalizations of manic patients in a psychiatric hospital in Belo Horizonte, 1996 to 2000.**

Treatments	N	%
Mood stabilizers:	125	88.6
Only Lithium	69	48.9
Only carbamazepine	23	16.3
Only valproate	0	0.0
lithium + carbamazepine	16	11.4
lithium + valproate	4	2.8
lithium + carbamazepine + valproate	1	0.7
Antipsychotics	115	81.6
Benzodiazepines	66	46.8
Antidepressants	5	3.6

**Table 4 - Different therapeutic schemes for the in-hospital treatment of mania, excluding ECT, in six observational studies.**

Items	Volpe et al, 2001 <sup>1</sup> N=284 1997	Goldberg et al, 1998 N=120 1991 to 1995	Sajatovic et al, 1997 N=96 1993 to 1995	Fenn et al, 1996 <sup>1</sup> N=129 1993 to 1994	Reetz-Kokott et al, 1996 N=68 1985 to 1987	Frye et al, 1996 <sup>1</sup> N=63 1987 to 1992
Mood stabilizers:						
Only lithium	44.4% <sup>a</sup>	54.2%	30.2%	43%	47.1%	60.5%
Only carbamazepine	13.7% <sup>b</sup>	5.8%	6.3%	18% <sup>g</sup>	13.2%	17.4%
Only valproate	5.3% <sup>c</sup>	10.8%	8.3%	38% <sup>g</sup>	0%	7%
Lithium + carbamazepine	20.7% <sup>d</sup>	16.7%	-	18% <sup>g</sup>	1.5%	7%
Lithium + valproate	5% <sup>e</sup>	10%	-	38% <sup>g</sup>	0%	2.3%
Antipsychotics	81.3%	88.3% <sup>f</sup>	74%	-	91.2%	-
Benzodiazepines	64.1%	88.3% <sup>f</sup>	-	-	-	-

a - Comparing data of the current study with the aggregated studies of Goldberg, Sajatovic, Fenn, Reetz-Kokott and Frye: N.S.

b - Comparing data of the current study with the aggregated studies of Goldberg, Sajatovic, Reetz-Kokott and Frye: N.S.

c - Comparing data of the current study with the aggregated studies of Goldberg, Reetz-Kokott and Frye: N.S.

d - Comparing data of the current study with the aggregated studies of Goldberg, Reetz-Kokott and Frye: X<sup>2</sup>= 16.2; p<0.001.

e - Comparing data of the current study with the aggregated studies of Reetz-Kokott and Frye: N.S.

f - 88,3% of the patients received either antipsychotics or benzodiazepines in this study (data not specified by the authors).

g - Including the use in association with other stabilizer (data not specified by the authors).

aesthetic drug to reduce the risk of post-ictal arrhythmias.<sup>6</sup>

The exclusively pharmacological interventions observed in this study were compared to those described in five recent observational studies of mania in the US and Germany<sup>14,18</sup> (Table 4). No significant difference was found in the rates of use of lithium in this sample, when compared to the data pooled from the reports of Goldberg et al,<sup>14</sup> Reetz-Kokkot & Müller-Oerlinghausen<sup>15</sup> and Frye et al<sup>17</sup> (71,1% vs. 70.3%;  $X^2=0.06$ ;  $p=0.812$ ).

The use of valproate (excluding ECT cases) was less frequent in our sample (11.6%), when compared to the pooled rate of 23.6% found combining the reports by Goldberg et al,<sup>14</sup> Reetz-Kokkot & Müller-Oerlinghausen,<sup>15</sup> Fenn et al,<sup>16</sup> Frye et al,<sup>17</sup> and Sajatovic et al<sup>18</sup> ( $X^2=16.8$ ;  $p<0.001$ ). This difference is even more striking when the comparison is made with the treatments used in the more recent American studies,<sup>16,18</sup> in which valproate was prescribed to 38.7% of the patients. The use of carbamazepine, among those patients who did not receive ECT, was more frequent in our sample than in the pooled data from Goldberg et al,<sup>14</sup> Reetz-Kokkot & Müller-Oerlinghausen,<sup>15</sup> Fenn et al,<sup>16</sup> and Frye et al<sup>17</sup> (35.2% vs. 20.6%;  $X^2=18.2$ ;  $p<0.001$ ). When focusing on the concomitant use of multiple mood stabilizers, the combination of lithium and carbamazepine was significantly more common in the present sample than in the pooled data from Goldberg et al,<sup>14</sup> Reetz-Kokkot & Müller-Oerlinghausen<sup>15</sup> and Frye et al.<sup>17</sup> (Table 4)

### Length of stay

The median length of stay was 15 days (CI 95% =14; 15) in this sample.

### Discussion

Naturalistic studies, as this, are useful in assessing the actual psychiatric practices, which may differ between countries. When comparing actual practices observed to those reported and/or recommended in the international literature, the authors sought to detect discrepancies, which potentially have implications for clinical and educational procedures.

Despite the increasing interest in other antimanic agents, it was found that lithium was the most frequently used mood stabilizer for inpatients in our sample and also on foreign reports.<sup>14-18</sup> This finding is consistent with the recommendations of the APA for the treatment of manic episodes<sup>19</sup> and reveals the major role that lithium still plays as an antimanic agent.

The relatively low frequency of the use of Valproate in the studied hospital is in disparity to its highly recommended use found in the American literature.<sup>20-22</sup> It is worth noting that valproate use in manic patients in the US was not approved in the US until 1995. This can explain the increasing proportion of patients treated with valproate in the more recent studies,<sup>16,18</sup> when compared to those published before 1993.<sup>14-16</sup> Carbamazepine appeared as the most frequently used anticonvulsant for the treatment of mania in the hospital under study, surpassing the use of Valproate, especially in association with lithium. It is interesting to note that, unlike valproate, carbamazepine has not yet been approved by the FDA for this indication. These findings suggest a possible lack of informa-

tion by local psychiatrists on recent research demonstrating the efficacy of valproate for the treatment of acute mania.<sup>20,21,23,24</sup>

The frequent use of carbamazepine in association with lithium might be explained by the severe and chronic profile of the cases of mania of our sample, indicating a higher probability of resistance to monotherapy.

The absence of Lamotrigine, Gabapentin and Topiramate among the observed prescriptions might be due to the fact that their antimanic efficacy has not been consistently demonstrated. The use of drug combinations is predicted in north-American guidelines for treating mania. Polipharmacy for the treatment of acute mania was observed in most of the studies reviewed and the present sample was no exception to this rule. This illustrates the great challenge controlling acute mania represents. A wide use of antipsychotic drugs was observed in all studies reviewed,<sup>14-18</sup> possibly indicating a concern with a rapid onset of antimanic effect which mood stabilizers cannot provide, due to their slower initial action.<sup>25</sup>

ECT was used in 33.2% of the admissions for mania included in this study. Only one other naturalistic study on the treatment of acute mania with ECT was found<sup>13</sup> in which a considerably smaller ratio of 8.5% is reported. In the large epidemiological study carried out in Ontario, Canada, by Malla,<sup>10</sup> 19.7% of the manic inpatients received ECT. The APA,<sup>19</sup> NIH<sup>7</sup> and the Canadian Psychiatric Association<sup>26</sup> recommend that ECT should be mostly used as a second-line antimanic treatment, which means it should be considered after the failure of the pharmacological treatment. Most of the clinical trials with antimanic agents report non-response rates over 30%.<sup>3,27</sup> The rate of ECT prescription observed in this study is consistent with these non-response rates to medication alone.

The higher rates of patients receiving ECT reported in this study could be related to the following: a) the hospital where it was performed is an institution for acute patients, which holds a 50-year-old tradition in using ECT. Therefore, those patients to whom ECT would be indicated might have preferably been admitted to this hospital, creating a possible selection bias; b) It is also a private institution, therefore, considering the evidence that ECT is considerably more often used in private hospitals than in university or public hospitals,<sup>28-30</sup> the discrepancies of results with those obtained by Black et al. and Malla, derived from university institutions might be explained. Anyhow, the rate of ECT use found in the present study reveals this is still an important therapeutical alternative for mania in local practice. ECT was administered using a sine wave device, which is considered obsolete. The international literature currently advocates the use of brief pulse devices, capable of provoking convulsion by means of a smaller amount of energy through the patient's brain and, thus, producing less undesirable cognitive side-effects.<sup>5,6,26</sup> The use of an obsolete device may possibly be linked to economic factors. It is worth noting that ECT had not yet been included in the List of Medical Procedures of the Brazilian Medical Association, and, therefore, was not properly valued by the private health care organizations, discouraging investments in more recent models. Differential values by these systems

when paying for procedures performed with brief pulse devices and the establishment of national guidelines for ECT practice are measures that could change this picture.

A striking feature of the psychiatrists' practice observed in this study was the high frequency in the concomitant prescription of lithium and ECT. Although some consider this association as dangerous and neurotoxic,<sup>1,31,32</sup> others view it as useful in the most difficult cases.<sup>33,34</sup> In the APA Guidelines for treating bipolar disorder, the safety recommendation is to discontinue the use of lithium before the onset of ECT.<sup>6</sup> Although the Royal College of Psychiatrists of Australia and New Zealand (RCPANZ) also recommends this safety procedure, it also admits that for some bipolar patients the risk of cycling overcomes that of delirium, and that in these cases, the association lithium plus ECT could be used.<sup>35</sup> In situations when the withdrawal of lithium is not advisable, a dose reduction has been proposed for safety.<sup>36</sup>

We can only speculate on the reasons for the divergences between this practice among the psychiatrists in this study and what the APA and the RCPANZ recommend. A possible explanation would be the mere lack of information on potential risks, since in Brazil there are no national regulations or set of guidelines as those existing in the US or Oceania. On the other hand, North-American authors, who are responsible for the majority of publications on the treatment of mania, might have excessive concern when using lithium, as other antimanic drugs have shown crescent status. In some cases, however, it is possible that this association might have been chosen for specific therapeutic purposes, since patients undergoing ECT are more often non-responsive to drugs and, thus, require more aggressive treatments. However, it is only fairly probable that this last hypothesis could account for the high proportion of cases (72.3%) in which the association lithium-ECT was used in this sample.

A frequent concomitant use of ECT with anticonvulsants (31.2%) and benzodiazepines (46.8%) was also observed. These medications increase the convulsive threshold and can hamper inducing therapeutic convulsions, or demand larger amounts of energy to provoke them, thus increasing the risk of cognitive side effects.<sup>5,6</sup> In order to avoid the adverse potential impact when using these drugs, it is advisable to reduce or suppress them before starting the course of ECT.<sup>5,6</sup> It is interesting to note that the average number of ECT sessions by course was smaller in the data studied than that reported for mania by other

authors.<sup>10-13</sup> This could suggest a synergetic effect in such frequent associations. Unfortunately, the design of this study does not allow the elucidation of this issue.

The choice of a given treatment strategy may be influenced by other factors, such as the chronic and resistant profile of manic episodes, the presence of medical and psychiatric comorbidities and also non-medical aspects (patient or parents' consent, availability of resources). These factors could not be taken into account in our study.

Median length of stay in this sample was 15 days, similar to what was reported by Frye et al<sup>17</sup> in a university institution (15.2 days) and lower than reported by Sajatovic et al<sup>18</sup> in a public hospital (24 days). Considering these results, the fact that the hospital in the present study was a private institution does not seem to have greatly influenced results. These data also indicate that the practices adopted in this hospital reflect a current trend of prioritizing outpatient treatment for affective disorders, once the acute crisis has been overcome. They also show that psychiatric admission, at least in the case of mania, does not necessarily imply long-term hospital permanence.

## Conclusions

The divergences found between the practices in treating mania observed in this study and those described and recommended by international publications and guidelines were: a less frequent use of valproate and a more frequent use of carbamazepine; the use of a sine wave device for performing ECT; and a broad concomitant use of ECT with lithium, anticonvulsants and/or benzodiazepines. These findings suggest that there is a need for developing national guidelines for the treatment of mania and for the use of ECT and their divulging in specific medical education programs, so as to standardize the procedures based on the available scientific evidence.

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