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FOUNDATIONS FOR THE TREATMENT OF BIPOLAR AFFECTIVE DISORDER IN ADULTS: INTEGRATIVE REVIEW

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Abstract: In order to identify in the literature the main therapeutic methods in the treatment of Bipolar Affective Disorder, in its various phases, in adults, an integrative literature review was carried out. Using the SciELO and LILACS databases, 8 articles were selected, published between January 2002 and January 2013. From these, two large groups of therapeutic approaches were delimited: (1) Pharmacological approach; (2) Non-pharmacological approach. Based on the literature, Olanzapine, ziprasidone, haloperidol and promethazine, haloperidol and midazolam and haloperidol are effective in controlling agitation and violent behavior through tranquilization after 12 hours, however, the combination of midazolam and haloperidol has the worst results among the others. In the prevention of new affective episodes, no medication has the level of evidence of lithium. Although the evidence for the efficacy of divalproate and carbamazepine in preventing recurrences remains uncertain, both are widely accepted as standard treatment for BAD. In addition, studies suggest that psychotherapy should be used in association with pharmacological treatment, as they promote a reduction in the frequency and duration of mood episodes, increased adherence to medication, a reduction in relapses and clinical impressions of general improvement.
Keywords: Bipolar Affective Disorder; Therapy; Adult.

INTRODUCTION

According to the World Health Organization (2001), 450 million people suffer from mental disorders, resulting from a complex interaction of genetic and environmental factors. Mental and behavioral disorders represent five of the ten leading causes of morbidity worldwide. The impact of these disorders has been evidenced by the fact that they represent four of the ten main causes of disability. In this context, Bipolar Affective Disorder (BAD) affects around 1.6% of the population and represents one of the main causes of disability worldwide (BLAZER, 2000).

BAD is a disorder characterized by significant mood swings between the poles of exaltation or euphoria (mania) and depression (SADOCK et al., 2007). Manic episodes are highly prone to recurrence. Around 75% of manic patients have more than one episode, and almost all patients with manic episodes also have depressive episodes (STUART et al., 2001). Recurrent episodes can cause deterioration in functioning and the number of episodes can have a negative impact on the prognosis of these individuals (KECK et al., 2001).

Modern neuroscience has made significant progress in understanding the brain mechanisms underlying Bipolar Affective Disorder (BAD). Recent studies have elucidated the importance of neurobiological regulation, including neuroplasticity and brain reward circuits, as crucial elements in the pathogenesis and treatment of BAD (Phelps et al., 2017).

The treatment of BAD involves management in the acute phases and maintenance therapy. Acute conditions require immediate containment of symptoms through pharmacology and, often, hospitalization to protect the patient. In the maintenance phase, in addition to drug therapy, the use of psychosocial treatment is indicated.

Thus, in order to identify the best therapy to be used in the treatment of BAD, the aim of this study was to identify in the literature the main therapeutic methods in the treatment of BAD, in its various phases, in adults.

METHODOLOGY

In order to achieve the objective, we opted for an integrative literature review, defined as a method through which research results are synthesized, enabling the categorization, analysis and evaluation of scientific knowledge already organized on the subject (URSI, 2005). The synthesis carried out by this research method allows the researcher to contextualize the topic, as well as identifying gaps in knowledge that need to be filled with new studies, contributing to discussions about methods and results of previous research (POLIT et al., 2006).

Genomic research has identified genetic variations that may influence susceptibility to BAD and response to pharmacological treatments. Candidate gene analysis and genome wide association studies (GWAS) have been instrumental in identifying loci associated with BAD (Craddock & Sklar, 2013).

To prepare an integrative review, the reviewer first determines the specific objective, formulates the questions to be answered and then conducts a search to identify and collect as many relevant primary studies as possible within the previously established inclusion and exclusion criteria (BEYEA et al. 1998). In order to guide this study, the following question was formulated: what is the therapeutic approach, described in the literature, used to treat BAD in adults?

For the bibliographic survey of this study, carried out in the last semester of 2010, an *online* search was made in the SciELO (Electronic Library of Brazilian Scientific Journals) and LILACS (Latin American Health Sciences Literature) databases. These databases were chosen because they include both national and international publications.

The following descriptors contextualized to the subject under study were used to survey the articles: (Bipolar Disorders OR Manic-Depressive Psychosis OR Bipolar Affective Psychosis OR Manic-Depressive Psychoses) AND (Treatment OR Therapy) AND (Adults).

According to the inclusion criteria proposed in the study, the articles had to be available in the databases indicated and strictly focused on the object of study. They had to have been published between January 2002 and January 2013, in Portuguese, English and Spanish, with abstracts and full texts. To check that the articles met the inclusion criteria, two independent reviewers assessed them and then compared them.

After reading the selected articles, the information was collected and entered into a database according to the following variables: year, methodological characteristics of the study, authors, objectives of the work, subjects studied - in terms of age and gender, results found and conclusion/final considerations of the study. All the records were stored in a specific file in the Microsoft program® Excel 2007.

RESULTS

SciELO identified 70 bibliographic references. After an initial analysis based on the inclusion criteria, reading the available abstracts and evaluating the question posed, 7 articles were selected. In LILACS, 59 references were identified and, following the same criteria, 1 article was considered. It should be noted that one article was found in both databases and was only considered once in the calculation of the texts included in the study. As a result, 8 articles were included in this review.

As for the study design, 4 (50%) were literature reviews, 2 (25%) were case-control studies, 1 (13%) was qualitative and 1 (13%) was cross-sectional. Of these, 5 (63%) were in Portuguese, 2 (25%) in English and 1 (13%) in Spanish. Regarding the year of publication, 1 (13%) was published in 2013; 1 (13%) in 2012; 2 (25%) in 2011; 2 (25%) in 2005 and 1 (13%) in 2004. The majority were published in Brazil, 6 (75%) and the rest in Colombia, 1 (13%); and Spain, 1 (13%). These data are summarized in Table 1.

AUTHOR	YEAR OF PUBLICATION	COUNTRY	METHODOLOGY
COLOM *et al.*	2013	Spain	Literature review study
COSTA *et al.*	2012	Brazil	Case-control study
MIASSO *et al.*	2011	Brazil	Qualitative study
BALDAÇARA *et al.*	2011	Brazil	Double-blind study
MORENO *et al.*	2005	Brazil	Literature review study
KNAPP *et al.*	2005	Brazil	Literature review study
LOTUFO NETO	2004	Brazil	Literature review study
NAVARRO BARRIOS *et al.*	2002	Colombia	Cross-sectional study

TABLE 1 - Identification of the studies selected for the integrative review. Governador Valadares, 2013.

From the texts studied, two main groups of therapeutic approaches were identified: Pharmacological Approach, 3 (38%) and Non-Pharmacological Approach, 5 (62%). In the group dealing with the pharmacological approach to the treatment of BAD, we can highlight articles demonstrating treatment in the acute phase (mania and hypomania) and the therapy phase. As for the non-pharmacological approach, there are examples of articles showing psychotherapeutic techniques and approaches to reduce symptoms, which are suggested as a complement to the pharmacological approach and, at times, as an important tool for improving adherence to treatment.

DISCUSSION

Hypomania and mania are common. Misdiagnoses and errors are common, so mental health professionals, as well as general practitioners, should be familiar with these syndromes to avoid delays in diagnosis and treatment, or inadequate treatment. Recently, new therapeutic options have improved the treatment of acute mania, especially the atypical forms, although lithium remains the first choice in acute mania. Others include valproate, carbamazepine and the available atypical antipsychotics, with an emphasis on olanzapine, followed by risperidone, which have the most evidence, taking into account preliminary results of the antimanic efficacy of aripiprazole, ziprasidone and quetiapine. Oxcarbazepine has been considered as a substitute for carbamazepine, assuming similar efficacy with a better tolerance profile (MORENO et al, 2005).

Advances in neuroscience reveal that dysfunction in neurotransmitter systems, particularly the dopaminergic and glutamatergic systems, is closely linked to the mood changes observed in BAD (Nestler et al., 2002). In addition, functional neuroimaging has demonstrated altered activity in regions such as the amygdala and prefrontal cortex during manic and depressive episodes (Phillips et al., 2008). In addition, the identification of genetic polymorphisms associated with BAD, such as variants in the CACNA1C and ANK3 genes, may eventually allow for personalized medicine, where specific treatments are adjusted based on the patient's genetic profile (Ferreira et al., 2008).

In the prevention of new affective episodes, no medication has the level of evidence of lithium. Although the evidence for the efficacy of divalproate and carbamazepine in preventing recurrences remains uncertain, both are widely accepted as standard treatment for BAD. In this sense, research favors olanzapine as the alternative agent of choice in preventive therapy (MORENO et al, 2005).

During the treatment of the acute phase of BAD, it was observed in the articles selected for this review that olanzapine, ziprasidone, haloperidol and promethazine, haloperidol

and midazolam and haloperidol are effective in controlling agitation and violent behavior through tranquilization after 12 hours. Patients receiving olanzapine during this phase of agitation had better control results, a lower percentage of excessive sedation and less need for mechanical restraint. Patients receiving ziprasidone had better results in controlling aggressive behavior, followed by haloperidol and promethazine. All the drug combinations have advantages and disadvantages, however the combination of haloperidol and midazolam has the worst results when evaluating the parameters of sedation, control of agitation and violence and side effects. In addition to the higher cost, atypical antipsychotics can be useful in emergency cases (BALDAÇARA et al., 2011).

During the drug therapy phase, after the events of the acute phase, some authors claim that there is ambivalence in relation to adherence to drug therapy for BAD (MIASSO et al. 2011). According to them, medication is placed in a general context of meanings, marked both by negative aspects such as suffering, illness, control, need, obligation, habit and guilt, and by positive aspects such as the possibility of socializing with people, crisis control, fewer readmissions and support. It also shows that there is a clear tendency to adhere to the medication after a long history of crises and hospitalizations, when the patient has already suffered several losses in different spheres of daily life. On the other hand, it is a fact that many of the side effects of medication are transient or can be minimized by different strategies, and that adequate guidance for patients and their families is essential to ensure adherence to treatment (MIASSO et al. 2011).

Although pharmacological treatment is essential in the treatment of BAD, there are still a substantial number of patients who, despite correct adherence to medication, remain symptomatic. Some of the studies listed here, regardless of the approach used, suggest that psychotherapy should be used in association with pharmacological treatment. Psychotherapeutic interventions have several benefits, including a reduction in the frequency and duration of mood episodes, an increase in medication adherence, a reduction in relapses and clinical impressions of general improvement (KNAPP et al. 2013).

Psychotherapeutic approaches should be individualized and used early on in the treatment of BAD in order to improve medication adherence and help the patient identify the basics of the illness with the aim of learning to develop strategies to cope better with such situations, as well as having an effect on residual symptoms which are associated with chronicity and high levels of suffering and disability (COSTA et al. 2012).

In addition to this approach, the use of psychoeducation as an additional prophylactic tool has recently been recognized by several prestigious treatment guidelines, broadening and updating the treatment paradigms for bipolar disorders. Clinicians should keep this in mind in their daily practice with BAD patients, especially since the benefits - in terms of fewer relapses and hospitalizations - are unquestionable and the cost is very low. To this end, there is an urgent need to train professionals in good communication skills and psychoeducational techniques in order to implement their use worldwide in bipolar disorders. Psychoeducation gives us a powerful tool not only to improve the outcome of our patients, but to help them manage despair, fears, stigma and low self-esteem. Psychoeducation should always be added to mood stabilizers, as it optimizes their effectiveness (COLOM et al. 2013).

FINAL CONSIDERATIONS

Based on the literature, Olanzapine, ziprasidone, haloperidol and promethazine, haloperidol and midazolam and haloperidol are effective in controlling agitation and violent behavior through tranquilization after 12 hours, however, the combination of midazolam and haloperidol is the one with the worst results among the others. In the prevention of new affective episodes, no medication has the level of evidence of lithium. Although the evidence for the efficacy of divalproate and carbamazepine in preventing recurrences remains uncertain, both are widely accepted as standard treatment for BAD. In addition, studies suggest that psychotherapy should be used in association with pharmacological treatment, as they promote a reduction in the frequency and duration of mood episodes, increased adherence to medication, a reduction in relapses and clinical impressions of general improvement. Developments in neuroscience and genomics are opening up new frontiers in the understanding and treatment of BAD. The future of BAD treatment may include approaches based on biomarkers that predict response to treatment and early intervention strategies that take into account individual genetic susceptibility.

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