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Carbamazepine in the treatment of bipolar disorder: a systematic review

Carbamazepina no tratamento do transtorno bipolar: uma revisão sistemática

DOI: 10.1590/0047-2085000000434

ABSTRACT

Objective: Expand knowledge on the role and efficacy of carbamazepine (CBZ) in bipolar disorder (BD), based on original studies. **Methods:** The authors performed a systematic review of the scientific literature on the efficacy of CBZ in BD, using the PubMed/MEDLINE, Web of Science (ISI), and SciELO databases. The search terms were: ("carbamazepine") AND ("bipolar" OR "mania" OR "manic"). There was no restriction on the year of publication. **Results:** A total of 27 articles were selected. Among the selected articles, 14 evaluated the use of CBZ in the manic phase of BD, two in the depressive phase of BD, and 11 in the maintenance phase of BD. In the studies on the manic phase of BD, CBZ proved superior to placebo (PLA). As for the depressive phase of BD, there were two studies, both with small samples. In the maintenance phase, CBZ was inferior to lithium, and no studies compared CBZ to PLA. **Conclusion:** The results of the clinical studies suggest that CBZ is effective for the treatment of the manic phase. Regarding the treatment of acute depression and maintenance of BD, the results of the studies indicate that there is not enough data demonstrating the effectiveness of CBZ.

KEYWORDS

Carbamazepine, bipolar disorder, systematic review, psychiatry.

RESUMO

Objetivo: Ampliar o conhecimento sobre o papel e a eficácia da carbamazepina (CBZ) no transtorno bipolar (TB), a partir de estudos originais. **Métodos:** Realizou-se uma revisão sistemática de literatura científica sobre a eficácia da CBZ no TB. Foram utilizadas as bases de dados PubMed/MEDLINE, Web of Science (ISI) e SciELO. Os termos de busca empregados foram: *("carbamazepine") AND ("bipolar" OR "mania" OR "manic")*. Não houve restrição quanto ao período de publicação. **Resultados:** Foram selecionados 27 artigos. Entre os artigos selecionados, 14 avaliavam o uso da CBZ na fase de mania do TB, 2, na fase de depressão do TB e 11, na fase de manutenção do TB. A CBZ, nos estudos na fase de mania do TB, mostrou-se superior ao placebo (PLB). Em relação à fase de depressão no TB, havia dois estudos não controlados e com amostras pequenas. Quanto à fase de manutenção do TB, a CBZ foi inferior ao lítio, e não foram realizados estudos comparando com PLB. **Conclusão:** Os resultados dos estudos clínicos sugerem que a CBZ é eficaz para o tratamento da fase de mania. Em relação ao tratamento de depressão aguda e manutenção do TB, os resultados dos estudos indicam que não há dados suficientes que demonstrem a eficácia da CBZ.

PALAVRAS-CHAVE

Carbamazepina, transtorno bipolar, revisão sistemática, psiquiatria.

Received in: May/7/2023. **Approved in:** Aug/7/2023

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INTRODUCTION

Anticonvulsants (ACs) such as carbamazepine (CBZ), lamotrigine (LAM), and valproic acid/divalproate (VA) are important options for the treatment of bipolar disorder (BD)[1,2]. LAM is only approved by the U.S. Food and Drug Administration (FDA) for the maintenance phase, although it is also commonly used in the depressive phase of BD[3,4]. Both CBZ and VA have only been approved by the FDA for the manic phase of BD[4]. The use of CBZ for BD in the United States is scarcely significant when compared to VA[5]. None of the main therapeutic guidelines for BD recommend CBZ as first-line therapy[3,6-8]. Meanwhile, VA is included among the principal options in the manic phase and maintenance treatment for BD[3,7,8]. However, evidence of the efficacy of VA in maintenance treatment is quite limited[9].

Recent years have witnessed few reviews on the use of CBZ in the treatment of BD. One such review[5], published in 2005, was not systematic and is already outdated. Another more recent review[10] only used one database and only included controlled studies. We conducted a systematic review of this topic, with three databases and a wider scope of original studies.

The objective of this systematic review was to expand the knowledge on the efficacy of CBZ in BD, based on original studies.

METHODS

We conducted a systematic review of the scientific literature on the efficacy of CBZ in the treatment of patients with BD. The review was registered in PROSPERO (International Prospective Register of Systematic Reviews) under number CRD 42022334472 and followed the Prisma Statement guidelines for systematic literature reviews and meta-analyses of studies that assess health interventions[11].

The review used the PubMed/MEDLINE, Web of Science (ISI), and SciELO databases, with the following search terms: ("carbamazepine") AND ("bipolar" OR "mania" OR "manic"). We use Mendeley Reference Manager as a reference manager. There was no restriction on year of publication. The search was performed by two independent researchers who reached a consensus at a second moment. Original studies were selected in which CBZ was used as monotherapy or in association in an episode of mania or bipolar depression or as maintenance therapy in BD. Only prospective studies were accepted. Finally, the study had to be published in English or Portuguese. The search was concluded on June 19, 2023.

RESULTS

Search and selection strategy

The initial search yielded 1,563 references in MEDLINE, 1,481 in Web of Science, and 9 in SciELO. There were 1423 duplicate references between the databases which were thus removed before the screening.

After reading the abstracts in the references, 125 articles were selected in PubMed and 48 articles in Web of Science. The main reasons for exclusion in this stage were: topic unrelated to treatment of BD: use of drugs other than CBZ; absence of original findings (review studies); and lack of evaluation of therapeutic efficacy.

After selection of the 173 articles (125 articles in PubMed and 48 articles in Web of Science), we reassessed the abstracts in the references, leading to the exclusion of 111 articles in this stage. The main reasons for exclusion of articles in this stage were: sample size less than 20 patients, language other than English or Portuguese, and retrospective method.

We selected 62 abstracts from the databases. These 62 articles were read in full. In this stage, 35 studies were excluded due to failure to meet the selection criteria: 14 case reports; three systematic reviews; nine with samples less than 20 patients; six with heterogeneous samples as to the BD phase; two retrospective studies; and one with a sample consisting exclusively of patients with schizoaffective disorder. In the end, 27 articles were selected. Figure 1 shows the flowchart for the article selection.

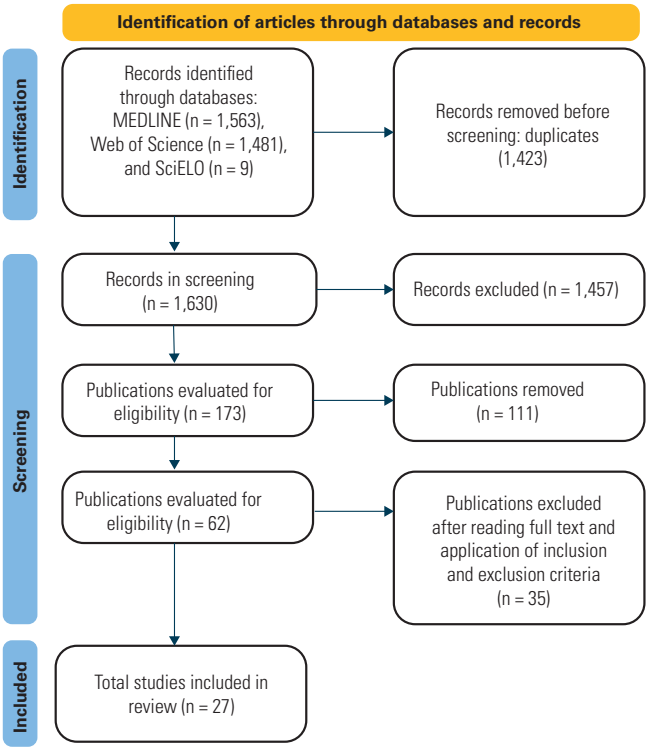

Figure 1. Article search and selection process. Source: Page et al. (2021)[11].

Studies involving children

Children were samples in three studies[12-14]. In one of them, the mean dose of CBZ was 788 mg/day and the mean age was 9.1 years[12]. In another of these studies the average dose ranges from 400 mg/day in the first week to 680 mg/day in the fourth week and the average age in that study was 15.40 years[13]. In the other study the average age was 13.4 years and the most prevalent dose of CBZ was 1,200 mg/day[14]. These three studies were about patients in the acute manic phase of BP[12-14].

Mania

Fourteen studies were found on the use of CBZ in the acute manic phase of BD, as shown in Table 1[12-25]. Twelve scales were used to evaluate manic symptoms[12-25], of which the most frequent were the Young Mania Rating Scale (YMRS)

Table 1. Efficacy of CBZ in the acute manic phase of BD

Study	Sample	Design	Method	Instruments	Results
Weisler et al. (2008)	N = 53, includes mixed state	CBZ-ER + atypical AP or Li	Uncontrolled study, 8 weeks	YMRS, HAM-D, MADRS	YMRS (mean - 12.9 pts.), HAM-D (– 5.1), MADRS (-7.4)
Joshi et al. (2010)	N = 27, includes mixed state, hypomania, all 6-12 years old	CBZ monotherapy	Uncontrolled study, 8 weeks	YMRS	52% patients, reduction > 30; 44% patients, reduction > 50; 34% patients, reduction >
Findling et al. (2014)	N = 157, includes mixed state, all 10-17 years old	CBZ monotherapy	Uncontrolled study, 26 weeks	YMRS	56.8% patients, reduction > 50%; 49% patients, remission of mania
SingH RK et al. (2019)	N = 67, all children and adolescents 6-17 years old	CBZ monotherapy	Uncontrolled study, 6 weeks	CSMS	Response rate, CBZ (70%)
Weisler et al. (2004)	N = 204, includes mixed state	CBZ-ER (N = 101), PLA (N = 103)	Randomized, double-blind, placebo controlled, 3 weeks	YMRS, CGI, HAM-D	CBZ-ER>PLA
Weisler et al. (2004)	N = 239, includes mixed state	CBZ-ER vs. PLA	Randomized, double-blind, placebo controlled, 3 weeks	YMRS, CGI, HAM-D	CBZ-ER>PLA
Okuma et al. (1990)	N = 105	CBZ (N = 51) vs. Li (N = 54)	Randomized, double-blind, placebo controlled, 4 weeks	FGIR/CPRG	CBZ = Li
Shafti and Kaviani (2018)	N = 50 (all mates)	CBZ-ER (N = 25) vs. Li (N = 25)	Randomized, double-blind, placebo controlled, 3 weeks	MSRS E CGI	CBZ-ER < Li
Small et al. (1991)	N = 48	CBZ (N = 24) vs. Li (N = 24)	Randomized, double-blind, placebo controlled, 8 weeks	SDMS-D&M, BPRS, HAM-D	CBZ = Li
Lusznat et al. (1988)	N = 54	CBZ (N = 27) vs. Li (N+27)	Multicenter, randomized, double-blind, placebo controlled, 6 weeks	BRMAS	CBZ = Li
Okuma et al. (1979)	N = 60	CBZ (N = 32) vs. CLP (N = 28)	Randomized, double-blind, placebo controlled, 3-5 weeks	CPRG	CBZ = CLP
Juruena et al. (2009)	N = 52 (includes hypomania)	CBZ+Li (N+26) vs. OXC+Li (26)	Single-center, randomized, double-blind, placebo controlled, parallel groups, clinical trial, 8 weeks	YMRS, HAM-D21, MADRS	CBZ + Li < OXC + Li
Tohen et al. (2008)	N = 134	CBZ+ OLZ (N = 58) vs. CBZ+PLA (N = 60)	Randomized, double-blind, placebo controlled, 6 weeks	YMRS, CGI, MADRS	CBZ + OLZ = CBZ + PLB
Weisler RH et al. (2008)	N = 111	CBZ-ER 2x/day (N = 58) vs. CBZ-ER 1x/day (N = 53)	Multi-center, randomized, double-blind, placebo controlled, parallel groups, 12 weeks	YMRS,CGI, HAM-D21, MADRS	CBZ-ER 1x/day = CBZ-ER 2x/day

Sources: Weisler et al. (2008)[18]; Joshi et al. (2010)[12]; Findling et al. (2014)[14]; Singh et al. (2019)[13]; Weisler et al. (2004)[19]; Weisler et al. (2004)[20]; Okuma et al. (1990)[21]; Shafti and Kaviani (2018)[22]; Small et al. (1991)[23]; Lusznat et al. (1988)[24]; Okuma et al. (1979)[15]; Juruena et al. (2009)[25]; Tohen et al. (2008)[16]; Weisler et al. (2008[17].

in eight studies[12,14,16-20], the Clinical Global Scale (CGI) in five[16,17,19,20,22], and the Hamilton Rating Scale for Depression (HAM-D) in four[18-20,23]. Sample size ranged from 27 to 239 patients[12,20]. Three studies had samples that only included children or adolescents[12-14]. The samples in five studies included patients in mixed state[12,14,18-20,22]. Ten were controlled[15-17,19-25] and four were uncontrolled[12-14,18]. All the controlled studies were randomized and double-blind[15-17,19-25]. Study duration varied from three to 26 weeks[14,19,20,22].

In four uncontrolled studies, CBZ led to an important reduction in manic symptoms in monotherapy[12-14] or in association with lithium or an antipsychotic AP[18]. In the controlled studies, CBZ in monotherapy was superior to placebo in two studies[19,20]; inferior to lithium in one study; but did not differ from it in three other studies[21-24]; and it was as effective as chlorpromazine (CLP)[15]. The combination of CBZ and lithium was inferior to the combination of oxcarbazepine (OXC) and lithium[25]. The combination of CBZ and olanzapine (OLZ) did not differ from the combination of CBZ and placebo[16]. Finally, one study showed that the efficacy of CBZ did not vary as a function of the number of times the drug was taken, i.e., once or twice a day[17]. Table 1 shows the studies' results in the manic phase of BD.

Acute depression

Table 2 shows the two studies on the use of CBZ in the acute depressive phase of BD[26,27]. Three scales were used to assess depressive symptoms[26,27]: Bunney-Hamburg Rating Scale (BHRS), Brief Psychiatric Rating Scale (BPRS), and HAM-D[26,27]. The sample sizes were 24 and 27 patients[26,27]. The studies' duration varied from three to eight weeks[26,27].

In the two uncontrolled studies, CBZ in monotherapy was associated with a high positive response rate, 62%[26] and 63%[27], respectively. Table 2 shows the results of the studies in the depressive phase of BD.

Maintenance

The review yielded 11 studies on the use of CBZ in maintenance treatment of BD, as shown in Table 3[16,28-37]. Fifteen clinical evaluation scales were used, the most common of which were the Bech-Rafaelsen Mania Scale (BRMAS)[28,34], Bech Rafaelsen Melancholia Scale (BRMES)[28,34], Goal Attainment Scale (GAS)[31,32], and CGI[29,34]. Among the scales, three assess depressive symptoms, two assess manic symptoms, and ten are not specific for either mania or depression. Sample size varied from 32 to 234 patients[35,37]. Eight studies were controlled[28,30-34,36,37], one of which was double-blind[28] and seven were not blind [30-34,36,37]. The controlled studies included six that were randomized[28,31-34]. Three studies were uncontrolled[16,29,35]. Study duration varied from 20 weeks to six years[16,35].

In three uncontrolled studies, CBZ in monotherapy or in association with lithium or an antipsychotic led to an important reduction in the relapse rate, which varied from 12.4% to 62.5% of patients[16,29,35]. In the controlled studies, CBZ in monotherapy was inferior to lithium in six studies[28,30-33,36] and did not differ from it in one study[34]; the association CBZ-Li did not differ from CBZ monotherapy[37]. Table 3 shows the results of studies in the maintenance phase of BD.

DISCUSSION

Overview

The current study is a systematic review of the scientific literature that analyzed articles with samples of at least 20 patients on the efficacy of CBZ in treatment of patients with bipolar disorder. The selected articles were divided among those addressing episodes of mania or bipolar depression and maintenance treatment of BD. In studies of the manic phase of BD, CBZ proved effective for the treatment of mania, highlighting two studies in which CBZ was superior to placebo. The findings of efficacy with CBZ monotherapy in acute mania phase refer to uncontrolled studies involving children or adolescents[12–14]. In studies involving adults the efficacy of CBZ in the acute mania phase could be associated with other approaches. The efficacy of CBZ in the acute manic phase is established better than in the depressive phase or in maintenance treatment of BD. CBZ proved effective according to two studies that analyzed the depressive phase of BD, but neither study was controlled and the samples were small. Furthermore, the studies were conducted more than 20 years ago, thus displaying low level of evidence for the use of CBZ for depression in BD. As for the maintenance phase of BD, CBZ was inferior to lithium. However, CBZ showed a positive response both in monotherapy and in association with other drugs for maintenance therapy in BD in various studies, most of which

Table 2. Efficacy of CBZ in the acute depressive phase of BD

Study	Sample	Design	Method	Instruments	Results
Post et al. (1986)	N = 24	CBZ monotherapy	Uncontrolled study, 8 weeks	BHRS and BPRS	CBZ: 62% positive response (15 of 24 patients)
Dilsaer et al. (1996)	N = 27	CBZ monotherapy	Uncontrolled study, 21 days	HAMD	CBZ: 63% positive response (17 of 27 patients)

Source: Post et al. (1986)[26]; Dilsaver et al. (1996)[27].

Table 3. Efficacy of CBZ in maintenance treatment of BD

Study	Sample	Design	Methods	Instruments	Results
Tohen et al. (2008)	N = 136	CBZ + OLZ	Uncontrolled, 20 weeks	YMRS, MADRS	9% patients, relapse depression, 3.4% patients, relapse mania
Ketter et al. (2004)	N = 92, patients with normal mood after treatment of acute mania	Non-comparative study	Uncontrolled, 6 months	YMRS, CGI, HAM-D, and time to relapse (primary endpoint)	Relapse: 14.3% patients; mean time to relapse, 61 days; discontinuation, 68.8% patients; prior improvement of YMRS, CGI, HAM-D maintained.
Kishimoto et al. (1983)	N = 32	CBZ or CBZ + (Li ou AP)	Uncontrolled, 6 years	Pre-treatment vs. post-treatment	No recurrence of episodes after start of treatment: 12.5% patients; lower recurrence after start of treatment: 62.5% patients; no change in recurrence after start of treatment: 25% patients
Hartong et al. (2003)	N = 94	CBZ (N = 50) vs Li (N = 44)	Randomized, double-blind, controlled, 2 years	BRMAS , BRMES e CPRS.	CBZ < Li
Kleindiesnst and Greil (2000)	N = 171	CBZ (N = 85) vs Li (N = 86)	Randomized, controlled, 2.5 years	GAS	CBZ < Li
Kleindienst and Greil (2002)	N = 171	CBZ (N = 85) vs Li (N = 86)	Randomized, controlled, 2.5 years	GAS	CBZ < Li
Greil et al. (1997)	N = 144	CBZ (N = 70) vs Li (N= 74)	Randomized, controlled, 2.5 years	RDC	CBZ < Li
Flechtner et al (1996)	N = 175	CBZ vs Li	Multi-center randomized, controlled, 2.5 years	TS and NS	CBZ < Li
Peselow et al (2016)	N = 225	CBZ (N = 50) vs Li (N = 98) vs VA (N = 77)	Open, 18 months	RDC, relapse	CBZ and VA< Li
Musseti et al. (2018)	N = 234	(CBZ or VA) (N = 56) vs Li + (CBZ or VA) (N = 127) vs Li (N=51)	Open, 18 meses	UFE	(CBZ or VA) < Li + (CBZ or VA) = Li
Simhandl et al. (1993)	N= 84	CBZ (low serum level, N=30) vs. CBZ (high serum level, N=28) vs. Li (N=26)	Randomized, controlled, 2 years	CGI, BPRS, BRMAS e BRMES	CBZ (low serum level) = CBZ (high serum level) = Li

Sources: Tohen et al. (2008)[16]; Ketter et al. (2004); Kishimoto et al. (1983); Hartong et al. (2003); Kleindienst and Greil (2000); Kleindienst and Greil (2002); Greil et al. (1997); Flechtner et al. (1996); Peselouw et al. (2016); Musseti et al. (2018); Simhandl et al. (1993).

Key for all the tables: N: number of patients in study; ">" superior response; "<" inferior response; "=" without statistical difference; ER: extended release; CBZ: carbamazepine; PLA: placebo; Li: lithium carbonate; VA: valproic acid; AP: antipsychotic; HAL: haloperidol; CLP: chlorpromazine; RIS: risperidone; GAB: gabapentin; QUE: quetiapine; ARP: aripiprazole; LAM: lamotrigine; OLZ: olanzapine; LEV: levetiracetam; OXC: oxcarbazepine; AMI: amitriptyline; TOP: topiramate

were quite old, uncontrolled, and with small samples. The analysis of the available articles on the use of CBZ in BD reveals a low number of studies. In addition, most of the existing studies were conducted more than five years ago and few were controlled, randomized, or double-blind or had adequate samples of patients followed for adequate length of time.

In 2005, Wang and Ketter[5] conducted a non-systematic review on the use of CBZ in BD. Their review only covered controlled studies. A new non-systematic review in 2021 by Grunze et al.[10] only used controlled studies in MEDLINE. Neither of the reviews accepted uncontrolled studies from different databases[5,10]. Both reviews concluded that CBZ is an effective option for the manic phase of BD[5,10]. The review by Grunze et al. concluded: that the data are insufficient to indicate CBZ for depression in BD; that the drug prevents episodes of mania; and that it is not responsible for exacerbation of depressive episodes[10]. The review by Wang and Ketter concluded that CBZ has a weaker antidepressant effect compared to its antimanic effect, and that it can be considered an effective drug in the prevention of acute relapses[5]. This review covers a larger number of original articles, using a larger amount of databases. Another important point of this review compared to the previous ones is that it was carried out through a systematized methodology. In addition, this review provides updated data regarding this topic.

Carbamazepine

Carbamazepine (CBZ) has been used as an antiepileptic drug since the 1960s in Europe and had its use approved for epileptic seizures in the 1970s in the United States[38]. It is generally used for neurological and psychiatric diseases[8,38], and its chemical structure is similar to that of tricyclic antidepressants such as imipramine[39]. The mechanism of action is not completely known, but studies indicate that CBZ binds mainly to sodium channels and interacts with calcium and potassium channels[40]. Other mechanisms that may also be associated are the decrease in glutamatergic excitatory effect and the increase in the inhibitory effect of gamma-aminobutyric acid (GABA)[40]. CBZ is mostly metabolized in the liver and its half-life is approximately 35 hours[41,42]. The drugs is metabolized primary by the CYP3A4 enzyme and induces its own metabolization, which leads to an increase in clearance and a decrease in the half-life, thus potentially requiring dose adjustments over the course of treatment. CBZ can also induce the biotransformation of other drugs[41-43].

Two drugs are derived from CBZ: OXC and eslicarbazepine (ESL)[44,45]. Most studies on the use of OXC in BD date to the 1980s and show that OXC has less scientific evidence than CBZ[10,46]. OXC is generally used as an option to CBZ in situations of intolerance to the latter's side effects[10]. In 2012, the first case report was published that suggested the efficacy of ELS for BD, but data from other studies with greater level of evidence did not prove benefits from the use of this drug for BD[10,47]. The extended release (ER) formulation of CBZ displays greater tolerability and adherence, which contributes to increased efficacy when compared to the immediate release formulation[48]. Only the CBZ-ER formulation has been approved by the FDA for BD[48], but other countries such as Japan, Australia, Canada, and most European countries have approved both the immediate and extended release formulations of CBZ for use in BD[49].

CBZ was first developed in 1957, but the FDA only approved its use for BD in 2004[5]. The reasons for this delay in the approval of CBZ are due to patent restrictions and the high cost for a drug to be approved by the FDA[5]. With the advent of CBZ-ER, protected by patent, new randomized, double-blind, placebo-controlled clinical trials were performed that improved the level of evidence for the use of CBZ in BD, culminating in the approval of CBZ-ER for the manic phase of BD[19,20].

The potential adverse effects of CBZ are drowsiness, dizziness, diplopia, leukopenia, agranulocytosis, hyponatremia, aplastic anemia, hepatitis, headache, difficulty in concentration, lack of coordination, fatigue, tremor, weight gain, sleep disturbance, cognitive changes, depression, and liver toxicity[41]. Drugs such as phenytoin, phenobarbital, primidone, rifampicin, efavirenz, and herbs such as St. John's wort accelerate the clearance of CBZ, leading to a decrease in its effect[50]. Drugs such as fluoxetine, nefazodone, trazodone, clarithromycin, fluconazole, isoniazid, ketoconazole, metronidazole, ritonavir, risperidone, quetiapine, verapamil, and diltiazem inhibit CBZ metabolism and lead to an increase in its plasma level[43].

In relation to the acute manic phase of BD, CBZ is recommended under the guidelines of the Canadian Network for Mood and Anxiety Treatments (CANMAT) as second-line monotherapy, despite having level-1 scientific evidence. Meanwhile, the combination of CBZ and lithium or VA appears as a third-line option[3]. The guidelines of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) recommend CBZ as an alternative treatment to the first-line options, and this same recommendation is made by the guidelines of the American Psychiatric Association (APA), with moderate level of clinical confidence[7,8].

As for mixed state of BD, CBZ-ER appears in the CANMAT guidelines as a third-line option for manic episodes with mixed characteristics, with level-4 evidence[6]. CANAMAT does not recommend CBZ for use in mixed episodes of BD with depressive characteristics[6]. In mixed episodes of BD according to the DSM-IV criterion, CBZ-ER is a second-line option with level-2 evidence and an option for use in association with VA, with level-4 evidence[6]. The RANZCP guidelines consider CBZ as a second-line alternative to the principal options for mixed cases that meet the criteria for both mania and depression. The APA guidelines present CBZ as an alternative to the first-line options with moderate level of clinical confidence for mixed states of BD[8].

According to the CANMAT guidelines, for acute depression in type I BD, CBZ monotherapy is recommended as a third-line option, with level-2 evidence. As for type II BD in acute depression, CBZ is not considered a treatment alternative[3]. The RANZCP guidelines recommend CBZ an alternative to the treatments of choice for acute depression in BD[7,8].

For maintenance treatment of type I BD, the CANMAT guidelines recommend CBZ as a second-line alternative for use in monotherapy, with level-2 evidence. As for the maintenance phase in type II BD, they recommend CBZ as a third-line option, with level-3 evidence[3]. According to the RANZCP, CBZ is considered an alternative to the first-line options for use in monotherapy. And the APA guidelines recommend CBZ as an alternative to the first-line options with moderate level of confidence for maintenance treatment of BD[7,8].

Other drugs in bipolar disorder

Other ACs such as LAM and VA play an outstanding role in BD[3]. VA is widely used in the manic and maintenance phases of BD, while LAM has been commonly used in the depressive and maintenance phases of BD[3]. Antipsychotics (APs) are also extensively used in the treatment of BD[3]. Risperidone and haloperidol are generally used in the manic phase of BD, aripiprazole is used in the manic and maintenance phases of BD, and OLZ as well as quetiapine are used in the manic, maintenance, and depressive phases of BD[3].

Comparison of carbamazepine and valproic acid

CBZ and VA began to be studied systematically for mood disorders in the second half of the 20th century due to reports of favorable psychotropic profiles in patients with epilepsy and observations of these drugs in mood disorders[51,52]. The use of CBZ in the United States is quite limited when compared to that of VA[5]. While VA was approved by the FDA in 1994 for use in acute mania, CBZ was only approved in 2004 for use in acute mania in the extended release formulation (CBZ-ER)[19,20]. One of the reasons why the FDA approved VA before CBZ for use in BD involved economic issues related to the fact that VA was patent-protected, while CBZ was not[5]. Controlled studies show that CBZ and VA are both superior to placebo and are as effective as lithium for acute mania in BD[53].

The FDA has only approved CBZ and VA for the acute manic phase, although VA has a more important role than CBZ according to various guidelines[4,6-8]. An example of this is the CANMAT guideline for BD, which recommends VA as first-line therapy in acute mania and maintenance treatment of BD and as second line in acute depression in BD[3]. Neither of the above-mentioned guidelines recommends CBZ as first choice[3,6-8].

Kindling

Kindling is a term used in epilepsy for elucidating convulsive disorders[49,54]. The kindling concept is based on discoveries that intermittent subliminal electric or chemical stimuli lead to progressively more intense depolarization in the brain[54]. In the 1970s, researchers postulated that the phenomenon could explain the episodic nature of BD[49,54]. The gradual and intermittent process of sensitization was seen to bear similarities to the episodic behavioral disorders in BD. Thus, the frequency and severity of mood disorders would increase gradually over time[54].

CONCLUSIONS

In short, the results of clinical studies suggest that CBZ is effective in the treatment of the manic phase of BD. Greater level of evidence is needed in relation to the depressive and maintenance phases of BD. Although CBZ is effective in the treatment of BD, the drug is not widely used in this disorder.

New double-blind, randomized, controlled studies are needed with adequate samples and follow-up, especially involving CBZ in the maintenance and depressive phases of BD, aimed at achieving greater level of evidence for the role of CBZ in BD.

INDIVIDUAL CONTRIBUTIONS

Vinícius Boaventura – Study conception and design, data analysis and interpretation, writing of the article, and approval of the final version for publication.

Rodrigo Rodrigues Lyrio – Study conception and design, data analysis and interpretation, and approval of the final version for publication.

Antônio Egidio Nardi – Study conception and design, and approval of the final version for publication.

Elie Cheniaux – Study conception and design, data analysis and interpretation, and approval of the final version for publication.

CONFLICTS OF INTERESTS

The authors hereby declare that they have no conflict of interest in this study.

ACKNOWLEDGEMENTS

The authors wish to thank the Instituto de Psiquiatria/ Universidade Federal do Rio de Janeiro (IPUB-UFRJ).

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