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Extended-release carbamazepine versus lithium in management of acute mania in male inpatients with bipolar I disorder

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ABSTRACT

INTRODUCTION: Since extended-release formulations of CBZ have been developed to decrease daily fluctuations in serum CBZ concentrations and improve dosing convenience, several large clinical trials have recently been conducted to assess the efficacy and tolerability of this form of CBZ in bipolar disorder. In the present assessment, extended-release carbamazepine has been compared with lithium, in a head-to-head evaluation, to assess its efficacy and safety in a group of non-Western patient population with diagnosis of acute mania.

METHOD: Fifty male inpatients with diagnosis of bipolar I disorder, according to *Diagnostic and statistical manual of mental disorders*, 5th edition (DSM-5), entered into a 3-week study, for random assignment to extended-release carbamazepine or lithium carbonate. The assessment had been accomplished as a double-blind design, while the patients, staff, prescribers, and assessor were unaware of the prescribed drugs that were packed into identical capsules. Primary outcome measure in the present assessment was Manic State Rating Scale (MSRS), which had been scored at baseline and weekly intervals up to the third week. Also, insight and overall illness severity and improvement had been rated by the Schedule for Assessment of Insight (SAI), Clinical Global Impressions-Global Improvement Scale (CGI-I), and Clinical Global Impressions-Severity Scale (CGI-S), respectively. Treatment effectiveness had been analysed by *t*-test and repeated measures analysis of variance (ANOVA). Statistical significance had been defined as *p*-value ≤ 0.05 .

RESULTS: While mean total score of MSRS improved significantly by both lithium and extended-release carbamazepine at the end of the third week, between-group analysis displayed significant advantage of lithium, regarding both frequency and intensity, at the end of trial. Mean total score of SAI showed significant improvement by both of them. However, again, the CGI-I demonstrated significant improvement by extended-release carbamazepine and lithium, CGI-S revealed significant progress only by lithium. Moreover, the effect size (ES) analysis showed large improvement of MSRS with lithium and medium improvement by extended-release carbamazepine. *Post hoc* power analysis showed an intermediate power of 0.42 on behalf of the present assessment.

CONCLUSION: Although both extended-release carbamazepine and lithium were helpful for improvement of manic symptoms, treatment with lithium seems to be more advantageous.

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Bipolar disorder; acute mania; lithium; tegretol CR; extended-release carbamazepine

Introduction

A manic episode is a distinct period of an abnormally and persistently elevated, expansive, or irritable mood lasting for at least 1 week or less if a patient must be hospitalized. An elevated, expansive, or irritable mood is the hallmark of a manic episode [1,2]. An untreated manic episode lasts about 3 months; therefore, clinicians should not discontinue giving drugs before that time [3,4]. The pharmacological treatment of bipolar disorders is divided into both acute and maintenance phases [5,6]. Bipolar treatment, however, also involves the formulation of different strategies for the patient who is experiencing mania or hypomania or depression [7]. Lithium, antipsychotics, and benzodiazepines have been the major approach to the

illness, but some anticonvulsant mood stabilizers, such as carbamazepine and valproate, have been added more recently as well as a series of atypical antipsychotics [8]. Lithium has been extensively studied in the treatment of acute mania and as maintenance therapy since the discovery of its mood-stabilizing properties more than 50 years ago, and it is currently considered to be a first-line treatment option in acute mania and prophylaxis in bipolar disorder. Nonetheless, despite its first-line status and its demonstrated overall efficacy in these settings, lithium therapy has been shown to be ineffective or poorly tolerated in a significant proportion of patients. In addition, it has a narrow therapeutic range and requires regular blood level monitoring, as severe or toxic effects can

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occur at twice the therapeutic dose [9]. Its narrow therapeutic range is an especially important consideration in older patients as their renal excretion becomes less efficient, resulting in an increased risk of lithium-associated toxic effects [9]. On the other hand, clinical evidence of the efficacy of carbamazepine in the treatment of bipolar disorder emerged in the early 1970s. At this time, several small studies reported the anti-manic effects of carbamazepine as well as its prophylactic effects against the recurrence of manic and depressive episodes in patients with bipolar disorder. Over the last several decades, many double-blind, controlled trials demonstrated the efficacy of carbamazepine in the treatment of acute mania in bipolar disorder, with response rates similar to those of lithium [10]. Early controlled trials of carbamazepine in the treatment of acute mania were conducted with conventional immediate-release formulations and confounded by co-administration with lithium or standard antipsychotics [10]. But, the established correlation between fluctuations in serum levels of carbamazepine and intermittent side effects helped prompt the development of extended-release formulations of carbamazepine for use in epilepsy. The subsequent use of extended-release carbamazepine in patients with epilepsy provided clinical evidence that, compared with immediate-release formulations, extended-release carbamazepine was associated with lower peak serum concentrations, decreased circadian toxicity, and decreased central nervous system side effects [10]. Since extended-release formulations of carbamazepine have been developed to decrease daily fluctuations in the serum concentration level of carbamazepine and improve dosing convenience, several large clinical trials have recently been conducted to assess the efficacy and tolerability of a novel, beaded, extended-release formulation of carbamazepine in bipolar disorder [10–12]. The beneficial effects of extended-release carbamazepine have been reviewed from different aspects by some other scholars as well [13,14]. In recent years, a new prolonged-release form of carbamazepine (tegretol CR) has been introduced in this region, which contains the active ingredient carbamazepine plus

cellulose-microcrystalline, silica-colloidal anhydrous, magnesium stearate, and supplementary elements. So, due to the limited database of RCTs on non-Western patients with acute mania, in the present assessment we compared extended-release carbamazepine with lithium, in a head-to-head comparison, to compare their efficacy and safety with each other.

Method

Fifty male inpatients with diagnosis of bipolar I disorder, according to *Diagnostic and statistical manual of mental disorders*, 5th edition (DSM-5) [15], who had been admitted to the hospital due to relapse or new emergence of an episode of acute mania, were entered into a 3-week, double-blind study, for random assignment to extended-release carbamazepine or lithium carbonate (Table 1 and Figure 1). The assessment had been accomplished as a double-blind design, while the patients, staff, prescribers, and assessor were unaware of the prescribed drugs that were packed into identical capsules. Division of patients had been done based on the last number of their ID card; even numbers into the extended-release carbamazepine group and odd numbers into the lithium group. While there was no specific financial support in this regard and funding was mainly through hospital infrastructure, the assessment started in February 2016 and ended in March 2017. Informed consent was given by the participant or a legal representative. The study was approved by the ethics committee of the academy. Suicidal ideation, mixed episode, severe aggression or instability, comorbid substance disorders, neurological and other severe medical illnesses, previous management with antidepressant medications, or long-acting antipsychotic (depot) drugs were among the exclusion criteria. While the patients in the first group ($n = 25$) were given prolonged-release tablets of carbamazepine (tegretol CR 200 and 400 mg divisible tablets, delivered by Novartis Pharma Services Inc.), the cases in the second group ($n = 25$) were prescribed lithium carbonate (generic form of 300 mg uncoated tablets). Both these medicines were given according to practice

Table 1. Demographic characteristics of participants.

Groups	Extended-release carbamazepine	Lithium	<i>t</i>	<i>p</i>	95%CI
Demographic variables					
Gender	Male (100%)	Male (100%)	–	–	–
Number	16	19	–0.71	.47	–0.32, 0.14
Age (yr)	33.71 ± 11.42 S.E.Mean = 2.85	28.64 ± 10.19 S.E.Mean = 2.34	1.388	.1745	–2.36, 12.50
Duration of illness (yr)	8.11 ± 3.65 S.E.Mean = 0.91	6.93 ± 4.18 S.E.Mean = 0.96	0.881	.3848	–1.55, 3.91
Number of prior episodes	5.57 ± 3.37 S.E.Mean = 0.84	4.14 ± 2.33 S.E.Mean = 0.53	1.479	.1487	–0.54, 3.40
MSRS (frequency), baseline	73.42 ± 11.33 S.E.Mean = 2.83	75.31 ± 9.47 S.E.Mean = 2.17	–0.538	.5943	–9.04, 5.26
MSRS (intensity), baseline	74.52 ± 10.62 S.E.Mean = 2.65	77.48 ± 11.27 S.E.Mean = 2.59	0.795	.4326	–10.54, 4.62

Note: MSRS: Manic State Rating Scale.

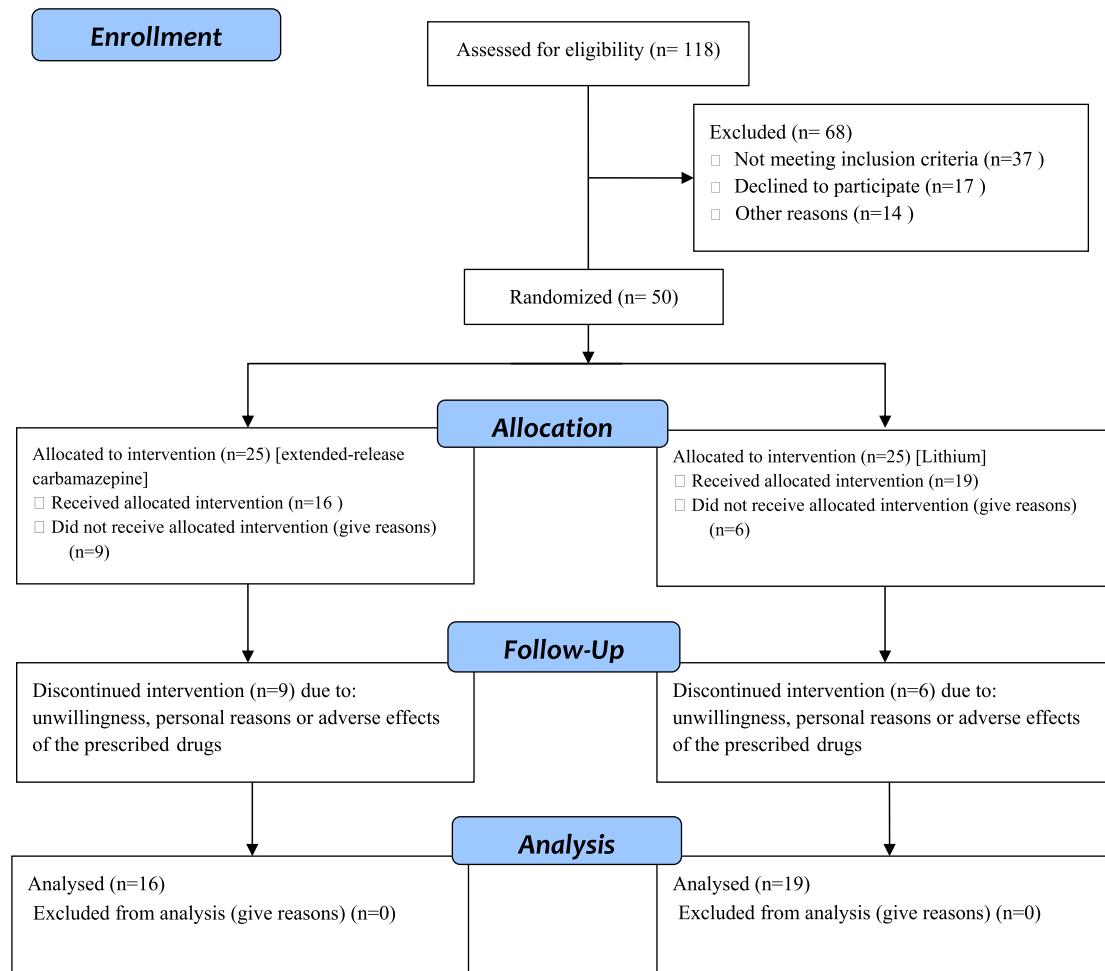


Figure 1. CONSORT flow diagram

guidelines and standard titration protocols. While prescription of lorazepam, as adjunctive medication, was permissible in the course of evaluation, no other anticonvulsant or supplementary antipsychotic was permissible during the trial. Moreover, except standard care, no extra psychosocial intervention was acceptable throughout the assessment. Primary outcome measure in the present assessment was the Manic State Rating Scale (MSRS), which had been scored at baseline and weekly intervals up to the third week [16]. MSRS is an instrument planned for measurement of severity of manic symptoms. The 26 items in this scale are each given a frequency score on a 0–5 gauge and an intensity score on a 1–5 gauge. Meanwhile, inter-rater reliability for each item has been reported to range from 0.89 to 0.99 [16]. Also, insight and overall illness severity and improvement had been rated using the Schedule for Assessment of Insight (SAI) [17], Clinical Global Impressions-Global Improvement Scale (CGI-I) [18], and Clinical Global Impressions-Severity Scale (CGI-S) [18], respectively. The aforesaid measures had been scored by the same experienced unaware psychiatrist in all cases. Mean modal dosages of extended-release carbamazepine and lithium in this trial were 912.5 ± 226.03 and 965.78 ± 172.48 mg/day, respectively. In addition,

mean serum level of lithium was 0.74 ± 0.17 milliequivalents per litre. Mean dosage of adjunctive lorazepam was 4.67 ± 1.30 mg/day for the extended-release carbamazepine group and 4.73 ± 1.63 mg/day for the lithium group, with no significant difference ($t = -0.119$, $p < .90$, 95%CI: -1.09 , 0.97).

Statistical analysis

MedCalc Statistical Software version 15.2 was used as a statistical software tool for analysis. Study had been done according to the “on-treatment” or “per-protocol” analysis, because the results of per-protocol analysis may provide a lower level of evidence, but better reflect the effects of treatment when taken in an optimal manner and is closer to a comparison of the true efficacies of the treatments than intention to treat analysis [19]. Patients were compared regarding baseline characteristics by means of *t*-tests, and treatment effectiveness, which had been assessed by MSRS, had been analysed by *t*-test and *repeated measures analysis of variance* (ANOVA) for intra-group analysis, and *Split-plot (mixed) design ANOVA* for between-group analysis. SAI, CGI-S, and CGI-I, which had been scored at baseline and the end of the third week, had been analysed by *t*-test. Also, *Cohen’s effect size* (ES)

for measurement of the strength of effectiveness and power of the study (*post hoc*) for evaluation of Type II error had been analysed. Statistical significance had been defined as p -value $\leq .05$.

Results

While nine patients (36%) in the extended-release carbamazepine group and six patients (24%) in the lithium group left the study during the first half of the assessment due to unwillingness, personal reasons, or adverse effects of the prescribed drugs, analysis for efficacy was based on data from a comparable number of patients in both groups ($z = -0.71$; $p < .47$; 95%CI = $-0.32, 0.14$). The groups were analogous regarding the baseline characteristics (Table 1). According to the findings, mean total score of MSRS improved significantly by both lithium and extended-release carbamazepine at the end of the third week (Tables 2 and 3 and Figures 2 and 3). Between-group analysis displayed significant advantage of lithium, regarding both frequency and intensity, at the end of the trial (Table 2). *Repeated measures analysis of variance* (ANOVA) showed

significant changes in frequency and intensity of MSRS by both medications [$F(3, 45) = 2.13$, $p < .041$, $SS = 281.62$, $MSe = 44.05$ and $F(3, 45) = 3.43$, $p < .024$, $SS = 398.06$, $MSe = 38.65$ for frequency, and $F(3, 54) = 5.61$, $p < .002$, $SS = 598.67$, $MSe = 35.58$ and $F(3, 54) = 5.56$, $p < .031$, $SS = 571.20$, $MSe = 34.21$ for intensity of symptoms, by tegretol CR and lithium, respectively]. *Split-plot (mixed) design ANOVA* also showed a significant difference in favour of lithium [$F(3, 144) = 2.95$, $p < .024$, $SS = 3141.91$, $MSe = 354.95$ for frequency, and $F(3, 144) = 2.90$, $p < .047$, $SS = 3055.03$, $MSe = 350.85$ for intensity of the symptoms, respectively]. Mean total score of SAI showed significant improvement by both of them (Table 3). However, again, the CGI-I demonstrated significant improvement by extended-release carbamazepine and lithium, CGI-S revealed significant progress only by lithium (Table 3). Moreover, since the sample size was not great, the *effect size* (ES) was analysed regarding alterations on the MSRS (frequency and intensity) at the end of treatment, which showed large improvement (" $d \geq 0.8$ " or " $r \geq 0.37$ ") with lithium and medium improvement (" $d \geq 0.5$ " or " $r \geq 0.24$ ") by extended-release carbamazepine

Table 2. Between-group analysis of primary outcome measure at the first, second, and third week.

Drugs Outcome measures	Extended-release carbamazepine ($N = 16$)	Lithium ($N = 19$)	t	p	95%CI
MSRS (frequency), week 1	72.02 \pm 7.89 S.E.Mean = 2.83	74.15 \pm 10.34 S.E.Mean = 2.83	-0.675	.5047	-8.55, 4.29
MSRS (frequency), week 2	71.52 \pm 8.32 S.E.Mean = 2.08	64.57 \pm 10.39 S.E.Mean = 2.38	2.155	.0386	0.39, 13.51
MSRS (frequency), week 3	65.53 \pm 10.67 S.E.Mean = 2.67	55.62 \pm 12.71 S.E.Mean = 2.92	2.470	.0189	1.75, 18.07
MSRS (intensity), week 1	73.66 \pm 9.91 S.E.Mean = 0.23	75.16 \pm 11.42 S.E.Mean = 2.62	-0.523	.6046	-7.34, 4.34
MSRS (intensity), week 2	71.28 \pm 8.49 S.E.Mean = 2.12	65.03 \pm 9.01 S.E.Mean = 2.07	2.099	.0436	0.19, 12.31
MSRS (intensity), week 3	66.14 \pm 11.73 S.E.Mean = 2.93	58.13 \pm 10.02 S.E.Mean = 2.30	2.180	.0365	0.53, 15.49

Note: MSRS: Manic State Rating Scale.

Table 3. Intra-group analysis of different outcome measures between baseline and third week, plus effect size analysis.

Drugs Outcome measures	Baseline	Week 3	t	p	95%CI	Cohen's d	Effect size r
MSRS (frequency), extended-release carbamazepine	73.42 \pm 11.33 S.E.Mean = 2.83	65.53 \pm 10.67 S.E.Mean = 2.67	2.028	.0515	-0.06, 15.84	0.71	0.33
MSRS (frequency), lithium	75.31 \pm 9.47 S.E.Mean = 2.17	55.62 \pm 12.71 S.E.Mean = 2.92	5.415	.0000	12.32, 27.06	1.7	0.65
MSRS (intensity), extended-release carbamazepine	74.52 \pm 10.62 S.E.Mean = 2.65	66.14 \pm 11.73 S.E.Mean = 2.93	2.118	.0425	0.30, 16.46	0.74	0.35
MSRS (intensity), lithium	77.48 \pm 11.27 S.E.Mean = 2.59	66.73 \pm 10.82 S.E.Mean = 2.48	2.999	.0049	3.48, 18.02	0.97	0.43
SAI, extended-release carbamazepine	2.31 \pm 1.17 S.E.Mean = 0.29	3.27 \pm 1.09 S.E.Mean = 0.27	-2.401	.0227	-1.78, -0.14	-0.84	-0.39
SAI, lithium	3.07 \pm 1.01 S.E.Mean = 0.23	4.29 \pm 1.48 S.E.Mean = 0.34	-2.968	.0053	-2.05, -0.39	-0.96	-0.43
CGI-S, extended-release carbamazepine	3.91 \pm 1.84 S.E.Mean = 0.46	2.88 \pm 1.03 S.E.Mean = 0.26	1.954	.0601	-0.05, 2.11	0.69	0.32
CGI-S, lithium	3.66 \pm 1.11 S.E.Mean = 0.25	3.01 \pm 0.16 S.E.Mean = 0.04	2.526	.0161	0.13, 1.17	0.81	0.37
CGI-I, extended-release carbamazepine	4.48 \pm 1.35 S.E.Mean = 0.34	3.61 \pm 1.01 S.E.Mean = 0.25	2.064	.0478	0.01, 1.73	0.72	0.34
CGI-I, lithium	4.66 \pm 1.12 S.E.Mean = 0.26	3.70 \pm 1.24 S.E.Mean = 0.28	2.504	.0169	0.18, 1.74	0.81	0.37

Note: MSRS: Manic State Rating Scale; SAI: Schedule for Assessment of Insight; CGI-S: Clinical Global Impressions-Severity Scale; CGI-G: Clinical Global Impressions-Global Improvement Scale.

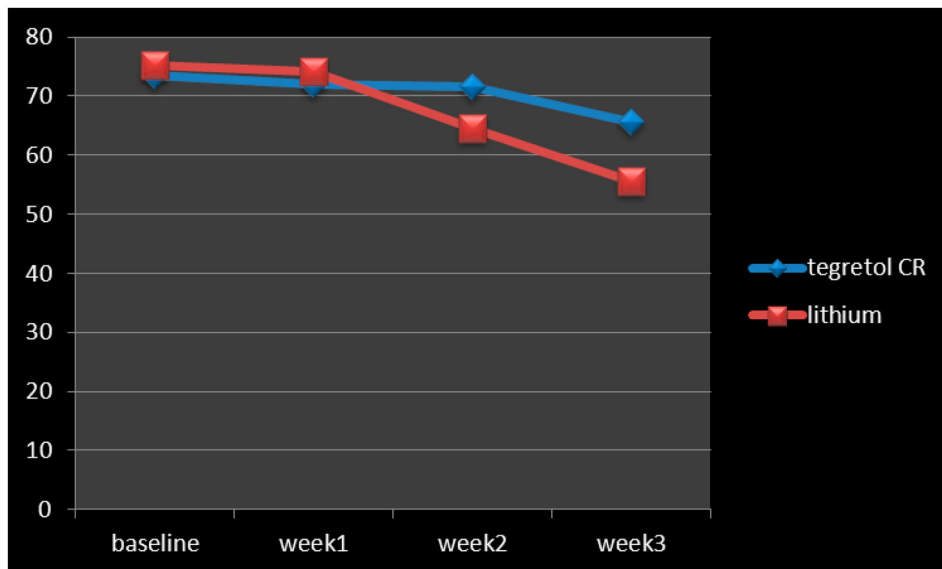


Figure 2. Changes of MSRS (frequency) between baseline and week 3.

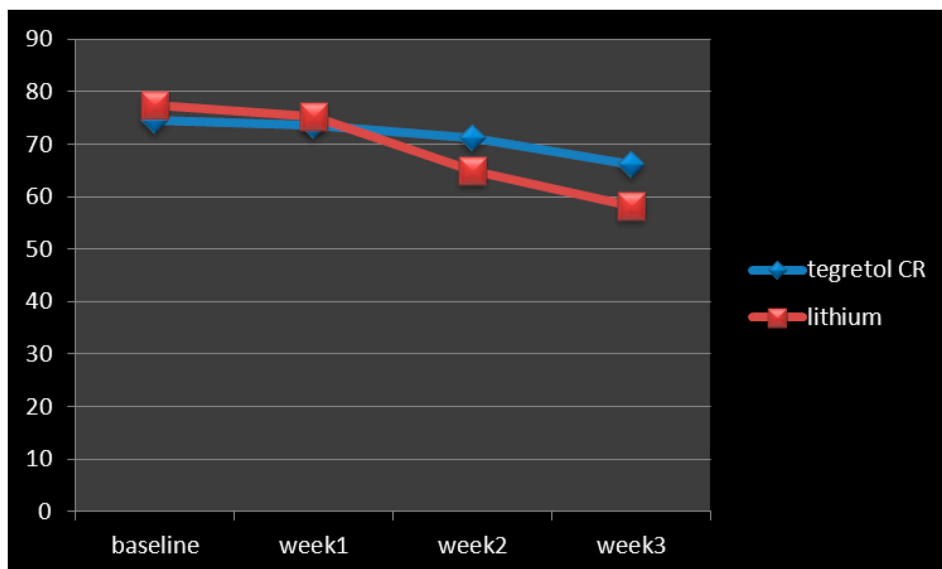


Figure 3. Changes of MSRS (intensity) between baseline and week 3.

(Table 3). *Post hoc* power analysis showed an intermediate power of 0.42 on behalf of the present assessment, which enhanced to power = 0.76 in the frame of compromise power analysis. The main reported side effects of extended-release carbamazepine in the related group were dizziness ($n = 6$; 16.66%), drowsiness ($n = 4$; 25%), and nausea ($n = 5$; 31.25%). Totally, 43.75% ($n = 7$) of the patients reported some kind of side effect upon the prescription of extended-release carbamazepine. The major adverse effect of lithium in the associated group was tremor ($n = 7$; 36.84%).

Discussion

Despite systematic guidelines for the treatment of bipolar disorder, the selection of appropriate therapeutic agents for use in conjunction with these guidelines

can be challenging, because the symptoms of bipolar disorder may be very different in different phases of the illness [20]. Especially, safety and tolerability are major factors in the selection of a therapeutic agent for bipolar patients [8]. With respect to the present study, while intra-group analysis showed that extended-release carbamazepine and lithium were significantly valuable in the improvement of frequency and intensity of manic symptoms, lithium was significantly more effective than extended-release carbamazepine, in the between-group analysis, after three weeks, which was clearly evident at the second week, too. Besides, based on available data and effect size analysis, maybe it could be stated that improvement in the lithium group was more evident than the other medication, particularly if statistical significance had been defined as $p\text{-value} \leq .01$. With regard to extended-

release carbamazepine, at least it is evident that our finding is relatively in complete agreement with the findings of Weisler et al., who had found monotherapy with extended-release carbamazepine capsules (ERC-CBZ; SPD417) in bipolar disorder patients with manic or mixed episodes, an effective therapeutic strategy [10,11]. But in the present assessment mixed episode was among the exclusion criteria. So, the effect of extended-release carbamazepine on depressive symptoms of manic episodes was not under survey. Also, extended-release form of carbamazepine in the current study was not exactly identical with the extended-release capsules used by Weisler and other scholars. Besides, while the sample size of Weisler et al. was large, its excessive drop rate, 42% of CBZ-ERC-treated patients and 50% of placebo-treated patients, somehow declines the power of study [10]. Also, while it was a large, randomized, double-blind, placebo-controlled parallel trial of carbamazepine monotherapy in acute mania, it was not a head-to-head comparison between extended-release carbamazepine and lithium, to compare their therapeutic outcomes. In addition, while the duration of the trials was identical, the primary outcome measures in these assessments were not analogous. Furthermore, while in the study accomplished by Weisler et al., CGI-I and CGI-S scores showed significant improvements from baseline for both manic and mixed patients at endpoint, it was not so for both of those sub-scales in the present trial. Likewise, the experience of adverse event by extended-release carbamazepine in our study was remarkably lower than what had been reported by Weisler et al., who had reported a high rate of adverse effects in their target group [10,11]. Actually, our experience with respect to side effects of extended-release carbamazepine was very similar to the standpoints of Fuller et al. [21] and Swainston Harrison et al. [22], who indicated that while the most frequent adverse effects associated with carbamazepine are somnolence, fatigue, dizziness, and headache, the most treatment-emergent adverse events observed with extended-release carbamazepine were of mild or moderate severity. Besides, viewpoints of Ginsberg, who had supposed that bipolar patients with more severe baseline symptoms are more likely to respond positively to this form of medications [23], sound right with reference to the proofs of the present study. On the other hand, with respect to the apparently advantageous effect of lithium, additional comparable outcomes are available. For example, while in some head-to-head comparisons, olanzapine was better than lithium [24] or similar to it [25], in another double-blind study on 40 inpatients meeting DSM-IV-TR criteria for acute mania, while both olanzapine and lithium were found to be significantly helpful in the improvement of manic symptoms, lithium was significantly more effective than olanzapine [26],

although it had been assessed in female subjects only. Also in another study, while both lithium and valproate were effective for improvement of manic symptoms, lithium was significantly more effective than valproate [27]. Likewise, though the results of several assessments strongly show that many anti-manic drugs are significantly more useful than placebo, their comparable effect sizes and overlapping confident intervals make it hard to determine that which one is better than the other. On the other hand, while in all the studies of combination therapy, the design was to add the second drug (vs. placebo) after two weeks of failure to adequately respond to a monotherapy, modern medical practice, generally influenced by additional factors such as cost and time, regularly use a combination of anti-manic agents, to bring mania under control as fast as possible – especially combinations of antipsychotics and mood stabilizers [8]. But there are actually no studies starting with combined therapy compared to a single agent. While practitioners have faith in these combinations getting people out faster, the evidence base is not really confirmative. In addition, comparative studies like this, employment of various outcome measures, different techniques of analysis, dissimilar durations of treatment, various sample sizes, different treatment dosages, and unlike patient cohorts (sex, age, duration of illness, number of episodes, smoking state, and pharmacological as well as other pre-treatments), plus pharmaco-genetic or ethnopsychopharmacologic factors should not be ignored, due to their possible influence on the results of the individual investigations. When we notice the similar findings regarding superiority of lithium over other SGAs [26] or mood stabilizers [27], we can conclude that the results of the present assessment regarding stronger effect of lithium on frequency and intensity of symptoms are nothing except than restating of an important clinical fact, which could have been overlooked due to hurried inferences. Although the fear of lithium toxicity and its narrow therapeutic index may encourage a lot of clinicians to choose more innocent medications, availability of precise laboratory checking of serum level of lithium and judicious employment of standard physical and laboratory checkups may encourage doctors to modify their perspective regarding lithium [28,29]. Further development of improved anti-manic drugs calls for agents with even better efficacy through clinical remission with better short- and long-term tolerability, as well as further testing of relative efficacy of existing compounds in more head-to-head, randomized comparisons [8]. Small sample size, short duration of evaluation, gender-based sampling, exclusion of mixed episodes, single-center design, low serum lithium levels (mean 0.7 mEq/Lt), lack of evaluation of carbamazepine levels, and lack of evaluations for comorbid ADHD and personality disorders were among the weaknesses of this trial.

Conclusion

Although both extended-release carbamazepine and lithium were helpful for improvement of manic symptoms, treatment with lithium seems to be more advantageous.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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