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Research Article

The Combined Use of Carbamazepine and Lithium in the Treatment of Outpatients with Rapid Cycle Bipolar Disorder without Psychiatric Comorbidity: Randomized, Double-Blind Placebo-Controlled Study

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Abstract

Objective: Rapid cycle bipolar disorder may be more resistant to treatment than other bipolar types. However, the effect of the combined use of carbamazepine and lithium in the treatment of outpatients with rapid cycle bipolar disorder without psychiatric comorbidity has not been studied in a double-blind placebo-controlled design. The study periods: from January 1, 2016 to January 2019. Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan.

Materials and methods: Eligible participants to meeting the DSM-5criteria for rapid cycle bipolar disorder was a double-blind, placebo-controlled trial, were required to be between 18 and 65 years. Response and side effects with carbamazepine and lithium and placebo were compared by using analysis of variance (ANOVA) and chi-square tests. The responder was con¬ducted by X2 ademonstrated superior for carbamazepine and lithium than for placebo. Carbamazepine and lithium was generally well tolerated by the patients in the study, although more carbamazepine and lithium -treated patients (n = 2) discontinued the study early because of adverse events.

Results: Twenty seven of the 36 combined use of carbamazepine and lithium -treated participants responded by 12 weeks, versus six of the 38 placebo-treated participant! ($p < 0.001$). The responder was con¬ducted by X2 demonstrated superior for carbamazepine and lithium than for placebo. Common side effects leading to discontinuation in the carbamazepine and lithium group were allergic reaction and drowsiness. Sweating and headache frequent complaint dur¬ing placebo treatment occurred in two of 38 men. There were not unexpected or serious adverse events.

Conclusions: The combined use of carbamazepine and lithium in the treatment of outpatients with Rapid cycle bipolar disorder demonstrated superior for carbamazepine and lithium than for placebo.

Key words: Rapid cycle bipolar disorder; carbamazepine; lithium; treatment.

1. Introduction

According the epidemiological data the prevalence of bipolar disorder DSM-5 over the course of 12 months and throughout life was 1.5% and 2.1% and did not differ between men (1.6% and 2.2%) and women (1.5% and 2 , 0%) [4].

Total spending on bipolar disorder type I (BDI) in 2015 was estimated at $ 202.1 billion, which corresponds to an average of $ 81,559 per person, while excess spending on BDI was estimated at $ 119.8 billion, which corresponds to an average of 48 333 USD per person [10].

The total cost of mental illness is estimated at more than 4% of GDP - or more than 600 billion Euros in 28 EU countries. Severe mental illness, such as bipolar disorder, affects nearly 5 million people (1.0% of the population), while schizophrenic disorders affect another 1.5 million people (0.3%) [20].

Available literature indicates that the pharmacological treatment of fast cycling is still scarce, and therefore there is no consensus on its optimal

pharmacological treatment. Clinical trials specifically studying rapid cycling are needed to unravel the proper management of bipolar disorder with rapid cycling [11]. Some authors conclude that rapid cycling is a common, albeit insufficiently recognized, condition for bipolar disorder, and it represents a worsening of the primary disorder. There is no convincing evidence that fast cycling is a separate subtype. Early recognition of this pattern can lead to an improvement in treatment strategy and an improvement in the long-term course. Conceptualizing fast cycling according to the results of these studies should be an important step forward [8].

Pharmacotherapy for rapid cycle bipolar disorder is an active area of research. A variety of drug groups have been shown to be effective in treating many of the rapid cycle bipolar disorder. From a therapeutic point of view, a previous study showed the effectiveness of several drugs. For example, lamotrigine is known to increase euthyma in patients with RCBD compared with placebo [13]. In addition, pramiprexol has been shown to facilitate resistant depression in patients with RBC [1]. In patients with concomitant pathological conditions, such as hypothyroidism, levothyroxine supplementation has been shown to eliminate the symptoms of RCBD in patients [9]. Finally, it has also been shown that ketamine is extremely useful in patients with RBC with active suicidal ideation [29]. Bipolar disorder is characterized by episodes of mood that almost always recur Patients who experience at least four episodes over a 12-month period are classified as "rapid cycles" . Patients who experience at least four episodes during a 12-month period are classified as "rapid cycling" [2]. The term was first used to describe bipolar patients who did not respond to lithium [20]. However, it is now clear that all drugs (including lithium) are less effective for patients with "rapid cycles" than patients with non-"rapid cycles" [29].

Rapid cycle bipolar disorder) may be more resistant to treatment than other bipolar types. In the open phase of the two-phase study, 133 depressed patients with rapid cycle bipolar disorder began to take lithium plus divalproex. Only 14% stabilized; 10% withdrew due to side effects; 17% were not committed. In the double-blind phase, 49 respondents were not randomized to placebo or lamotrigine. The two groups showed no differences in response rates. [20].

Studies show that the rapid cycle is different from other forms of bipolar disorder. People with such mood changes may respond differently to standard and experimental treatments than other people with bipolar disorder. With his sudden and unpredictable mood changes, rapid cycles can be more difficult than other types of bipolar disorder.

For rapid cycling (can be used for bipolar disorder I or bipolar disorder II): at least four episodes of mood during the previous 12 months that meet the criteria for a manic, hypomanic or major depressive episode. Episodes are limited to partial or complete remission for at least 2 months or a transition to an episode of opposite polarity (for example, an episode with major depression to a manic episode). An essential feature of bipolar disorder with rapid cycling is the occurrence of at least four episodes of mood over the previous 12 months. These episodes can occur in any combination and order. Episodes should meet the criteria for both the duration and the number of symptoms for a major depressive, manic, or hypomanic episode and should be limited to either a period of complete remission or a transition to an episode of opposite polarity. Manic and hypomaniac episodes are considered to be at the same pole. Except for the fact that they occur more often, the episodes that occur in the fast-cycle pattern are no different from the episodes that occur in the non-rapid -cycle mode. The episodes of mood that are taken into account when determining the fast cycle pattern exclude those episodes that are directly caused by the substance (for example, cocaine, corticosteroids) or another disease [2].

The crucial issue is demonstrated by reviewing the literature that the effect of the combined use of carbamazepine and lithium in the treatment of outpatients with Rapid cycle bipolar disorder without psychiatric comorbidity has not been studied in a double-blind placebo-controlled design. This study reports on a randomized, double-blind, placebo-controlled of carbamazepine and lithium in the treatment of outpatients with Rapid cycle bipolar disorder. The aim of this work was to study the effectiveness of carbamazepine in combination with lithium in the treatment of rapid-cycle bipolar disorder in the framework of type I bipolar disorder.

2. Materials and methods

This was a double-blind, placebo-controlled trial for patients diagnosed with DSM-5for rapid cycle bipolar disorder. The patients gave their informed, written consent to participate.

In accordance with the Helsinki Declaration of the World Medical Association "Recommendations for doctors engaged in biomedical research involving people", adopted by the 18th World Medical Assembly (Finland, 1964, revised in Japan in 1975, Italy - 1983, Hong Kong - 1989, the South African Republic - 1996, Edinburgh - 2000); The Constitution of the Republic of Azerbaijan, the Law "On Psychiatric Assistance" (adopted on 12.06.2001, with amendments and additions - 11.11.2011, Decisions of the Cabinet of Ministers of the Republic of Azerbaijan No. 83, dated April 30, 2010 "On Approval of the Rules for Conducting Scientific, Preclinical and Clinical studies of medicines" are established. The conditions of the conducted researches corresponded to the generally accepted norms of morality, the requirements of ethical and legal norms, as well as the rights, interests and personal dignity of the participants of the studies were observed.

The study periods: from January 1, 2016 to January 2019. Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan.

Also we excluded sexually active subjects with active or unstable epilepsy, other genetic syndromes or congenital infections associated with autistic-like syndromes, prematurity; subjects who have been treated within the previous 30 days by any medication known to have a clearly defined potential for toxicity or with any psychotropic drugs; subjects with clinically significant abnormalities in laboratory tests or physical examination; subjects with a history of hypersensitivity or serious side

effects associated with the use of carbamazepine and lithium, and subjects who, during the previous 3 months, started new non-pharmacological procedures, such as diet, vitamins and psychosocial therapy. A detailed clinical interview with parents by a clinical expert, accompanied by physical examination and blood analysis, was used to ensure that subjects did not meet any exclusion criteria.

This was a double-blind, placebo-controlled trial for patients diagnosed with DSM-5 for rapid cycle bipolar disorder. A structured clinical interview, for DSM-5Axis I Disorder, Patient Edition, was used to diagnose rapid cycle bipolar disorder according to DSM-5. Eighty patients (40 men and 40 women) whom we studied were under observation in Mental Clinic for Outpatients of Baku City of Azerbaijan Republic. The length of the washout was 2 weeks. Patients were washout from the all medications. The method of randomization was given by lottery. Each patient was randomized to receive either combined use of carbamazepine and lithium (40 patients) accordingly, in doses of 200 mg three times and 300 mg three times per day for 12 weeks or matched placebo (48 patients) in a double-blind manner. All patients were evaluated by experienced clinicians. The average level of concentration of carbamazepine and lithium in the blood plasma in patients was 7.8 ± 5.9 μg / ml and 0.6 - 0.8 mmol / l, respectively, range.

Eligible participants, in addition to meeting the DSM-5criteria for rapid cycling bipolar disorder and were required to be between 18 and 65 years of age. We excluded serious medical conditions including with other psychiatric disorders (e.g. bipolar disorder II tipi, schizophrenia, patients judged to be at serious suicidal or homicidal risk, dependence of psixoaktive drugs, somatic, neurological illness et c). Also we excluded unstable epilepsy, other genetic syndromes or congenital infections associated with autistic-like syndromes, prematurity; subjects who have been treated within the previous 30 days by any medication known to have a clearly defined potential for toxicity or with any psychotropic drugs; subjects with clinically significant abnormalities in laboratory tests or physical examination; subjects with a history of hypersensitivity or serious side effects associated with the use of carbamazepine and lithium, and subjects who, during the previous 3 months, started new non-pharmacological procedures, such as diet, vitamins and psychosocial therapy. A detailed clinical interview with parents by a clinical expert, accompanied by physical examination and blood analysis, was used to ensure that subjects did not meet any exclusion criteria.

Patients clinically significant of abnormal laboratory or EEG findings were ineligible. Patients before the study had used antidepressants, antipsychotics, anxiolytics, benzodiazepines, SSRI and venlafaxine. Washout of all medicines was two weeks.

Analysis of response refers to the last observation carried forward for all subjects who had valuables efficacy at baseline and with treatment. The responder analysis was conducted by using the chi-square (x^2) and analysis of variance (ANOVA) according to Glantz [30].

3. Results

Characteristics of the patients randomly assigned to the two treatments are shown in table 1.

Characteristic	Carbamazepine + lithium *n* =40	Placebo *n* = 40
	Mean SD	Mean SD
Age (years)	38.0 ± 10.2	37.4 ± 9.8
Duration of illness	10.2 ± 6.0	10.0 ±5.8
	n = 40%	*n* = 40%
Education:		
— primary school	28 (70)	30 (75)
— secondary school	12 (30)	10 (25)
Marital status:		
— never married	10 (25)	10 (25)
— married	20 (50)	18 (45)
— divorced	10 (25)	12 (30)
or separated		
Employment status		
— unemployed	18 (45)	20 (50)
— employed	22 (55)	20 (50)

Table 1. Sociodemographic characteristics of patients with rapid cycle bipolar disorder.

Note: differences between groups are not significant.

Statistical differences between the two groups are no significantly. The results of treatment are shown in Table 2. As shown from the Table 2, six patients did not return for at least one subsequent assessment, leaving 74 patients. (36 taking carbamazepine and lithium and 38 taking placebo) in the valuables study group.

The responder was conducted by X^2 demonstrated superior for carbamazepine and lithium than for placebo (Table2). Carbamazepine and lithium was generally well tolerated by the patients in the study,

although more carbamazepine and lithium -treated patients (n = 2) discontinued the study early because of adverse events. The two common side effects leading to discontinuation in the carbamazepine and lithium group were allergic reaction and drowsiness. Sweating a frequent complaint during placebo treatment occurred in two of 38 men. There were not unexpected or serious adverse events

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Treatment Groups	Observed number	Expected number	chi-square (x^2)
	Yes improvement*	Not improvement*	Total
Placebo	6 (16.43) 26	32 (21.57)	38
Carbamazepine + lithium	27 (15.56)	9 (20.43)	36
Total	33	41	74

Table 2. The results of the square analysis.

Note: expected numbers indication in the brackets. $X^2 = 22.68$, df (degree of freedom) = 1, $p < 0.001$.

Of the 38 placebo groups, only 6 (Yes improvement *) patients had intermission over three years. Not improvement * - In 32 patients with placebo groups, no intermission was observed.

Carbamazepine + lithium group of patients: of 36 patients, 27 patients experienced intermission for three years (Yes improvement *). Not improvement * - Carbamazepine + lithium group of patients: only 9 patients did not experience intermission.

4. Discussion

History and Discovery, structure–activity relationships, pharmacological profiles, mechanisms of action, pharmacokinetics and disposition, indications and efficacy response, side effects and toxicology, drug–drug interactions lithium and carbamazepine are described in detail in the literature [29]. Therefore, we will not dwell on them.

To our knowledge, this is the first report of a randomized, double-blind, placebo-controlled study of a Carbamazepine + lithium in the treatment of outpatients with Rapid cycle bipolar disorder without psychiatric comorbidity. Our data suggest that Carbamazepine + lithium) is efficacious in the management of rapid cycling bipolar disorder, as the participants had a clinically and statistically significant improvement in rapid cycling bipolar disorder over 12 weeks of treatment.

From the eighty patients six patients did not return for at least one subsequent assessment, leaving 74 patients (36 Carbamazepine + lithium and 38 taking placebo) in the valuables study group. Twenty six (94%) of the 36 Carbamazepine + lithium treated participants responded by 12 weeks, versus six (16%) of the 38 placebo-treated participants. The most common and problematic side effect in the carbamazepine and lithium group was on one allergic reaction and drowsiness. As a side effects in the placebo group indicated headache and sleeplessness.

As noted at the beginning pharmacotherapy for rapid cycle bipolar disorder is an active area of research. Pharmacotherapy for rapid cycle bipolar disorder is still very relevant [15, 21,24].

Our data partially coincide with some results of studies by other authors [13, 16]. It was found that carbamazepine has very limited possibilities in the treatment of rapid cycles, especially in the form of monotherapy. It has moderately pronounced effectiveness in the manic phase and weakly moderately effective in the depressive phase. [5].

At least 8 placebo-controlled randomized trials have demonstrated that lithium is a prophylactic in bipolar disorder. [21]. A meta-analysis of 16 studies of bipolar disorder conducted by Tondo and colleagues [29]. Tondo L, Hennen J, Baldessarini RJ. showed that lithium can be considered first-line treatment in the prevention of rapid cyclic bipolar disorder. Many studies confirm the effectiveness of lithium as a mood stabilizer [3, 7, 11, 19, 22, and 29].

Despite the obvious limitation of this study due to the small number of samples, we can argue that it shows promising data on the usefulness of the combined use of carbamazepine and lithium in the treatment of outpatients with Rapid cycle bipolar disorder in the routine treatment of complex pathologies in this illness. It will be important to explore further effects of the combined use of carbamazepine and lithium in the treatment of rapid cycle bipolar disorder

Conclusion of the article

As indicated earlier, rapidly recurring bipolar disorders are difficult to treat. Treatment should be based on current practical guidelines and expert advisory groups on the treatment of bipolar disorder. Historically, rapid cycles usually did not respond to lithium or carbamazepine. The long-term result of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients in a lithium clinic. Data from the largest prospective, placebo-controlled, rapid-cycle bipolar disorder study demonstrated the efficacy of lamotrigine in patients with euthyma or mood episodes. Used a 6-week titration of lamotrigine to 200 mg / day. The results of these data showed that lamotrigine monotherapy was a useful treatment, especially for patients with rapid- cyclic bipolar II disorder [20, 21]. More recent comparisons of lithium and valproic acid show no significant differences in efficacy between lithium and divalproate for long-term treatment of raipd-cycle bipolar disorder, but have shown that lamotrigine has the potential to complement both drugs in the treatment of depression [6].

Our Follow-up observation (catamnesus) was conducted from January 01, 2016 to July 01, 2019. The results of follow-up observations showed that patients receiving carbamazepine in combination with lithium are in a state in full remission during for 3 years.

Recommendation:

1. As indicated earlier, rapidly recurring bipolar disorders are difficult to treat. Treatment should be based on current practical guidelines and expert advisory groups on the treatment of bipolar disorder.
2. The combined use of carbamazepine and lithium in the treatment of outpatients with Rapid cycle bipolar disorder demonstrated superior for carbamazepine and lithium than for placebo.
3. Carbamazepine and lithium - drug interactions must be considered.
4. Availability a history of allergic reactions must be considered.

Limitation of the study: 1) the study must be carried out on a large number of populations; 2) the study must be carried out separately for women and men; 3) study intermission duration of more than five years.

Author Disclosure Information

The authors declare that the article is submitted on behalf of all authors. None of the material in the article has been published previously in any form and none of the material is currently under consideration for publication elsewhere other than noted in the cover letter to the editor. Authors declare no financial and personal relationship with other people or organizations that could inappropriately influence this work. All authors contributed to and have approved the final article. The authors declare no conflicts of interest. No sponsor provided funding for this study. Mental Health Center of the Ministry of Health of the Republic of Azerbaijan provided the outpatient unit, the material for clinical and neuro-psychological assessments, and electronic resources.

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References

1. Aditya H, Aditi S, Malvika R, Janardhanan C N, Suresh Bada M. Pramipexole in the treatment of refractory depression in a patient with rapid cycling bipolar disorder. Indian J Psychol Med. 2015;37(4):473-4.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.
3. Baldessarini RJ, Tondo L, Hennen J, et al. Is lithium still worth using? An update of selected recent research. Harv Rev Psychiatry. 2002;10:59-75. Abstract Baldessarini RJ, Tondo L, Hennen J, et al. Is lithium still worth using? An update of selected recent research. Harv Rev Psychiatry. 2002;10:59-75. Abstract.
4. Blanco C, Compton WM, Saha TD, Goldstein BI, Ruan WJ, Huang B, Grant BF, Epidemiology of DSM-5 bipolar I disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions – III, *Journal of Psychiatric Research* (2016), doi: 10.1016/j.jpsychires.2016.10.003.
5. Calabrese JR, Fatemi SH, Kujawa M, and et al. Predictors of response to mood stabilizers. J Clin Psychopharmacol. 1996 16(suppl). 24–31. [PubMed] [Google Scholar].
6. Calabrese et al., Calabrese, JR, Rapport, DJ, Youngstrom, EA, Jackson, K., Bilai, S. & Findling, RL (2005). New evidence on the use of lithium, divalproate and lamotrigine in fast cycles of bipolar disorder. European Psychiatry, 20, 92–95.
7. Calabrese JR, Shelton , Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Ganocy SJ, Findling RL. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. Am J Psychiatry. 2005 Nov;162(11):2152-61.
8. Carvalho AF, Dimellis D, Gonda X, Vieta E, Mclntyre RS, Fountoulakis KN. Rapid cycling in bipolar disorder: a systematic review.J Clin Psychiatry. 2014 Jun; 75(6):e578-86. doi: 10.4088/JCP.13r08905.
9. Chen P, Huang Y. Remission of classic rapid cycling bipolar disorder with levothyroxine augmentation therapy in a male patient having clinical hypothyroidism. Neuropsychiatr Dis Treat. 2015;11:339-42.
10. Cloutier M, Greene M, Guerin A. et al. The economic burden of bipolar I disorder in the United States in 2015. Journal of Affective Disorders 226 (2018) 45–51, http://dx.doi.org/10.1016/j.jad.2017.09.011.
11. Fountoulakis KN, Kontis D, Gonda X, Yatham LN. A systematic review of the evidence on the treatment of rapid cycling bipolar disorder. Bipolar Disord. 2013 Mar;15(2):115-37. doi: 10.1111/bdi.12045.
12. Dunner DL, Fieve RR. Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry. 1974;30:229-233. Abstract.
13. Goldberg JF, Bowden CL, Calabrese JR, Ket- ter TA, Dann RS, Frye MA, et al. Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. Biol Psychiatry. 2008;63(1):125-30.
14. Goodwin FK. Rationale for long-term treatment of bipolar disorder and evidence for long-term lithium treatment. J Clin Psychiatry. 2002;63(suppl 10):5-12. Abstract.
15. Huber J, Burke D. ECT and lithium in old age depression - Cause or treatment of rapid cycling? Australas Psychiatry. 2015;23(5):500-2.
16. Jonathan Silver & Kemp DE et al. Bipolar Disord 2012 Nov Nielsen J et al. Bipolar Disord 2012 Oct 26 Poon SH et al. Bipolar Disord 2012 Sep.
17. KAPLAN & SADOCK'S Synopsis of Psychiatry Behavioral Sciences/Clinical Psychiatry. 11th edition. Wolters Kluwer. 2015. 1499 pages.
18. Kemp DE, Gao K, Fein EB, Chan PK, Conroy C, Obral S, et al. Lamotrigine as add-on treatment to lithium and divalproex: lessons

learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder. Bipolar Disord. 2012;14(7):780-9.

19. Koukopoulos A, Reginalsi D, Laddomada P. Course of the manic-depressive cycle and changes caused by treatments. Pharmacopsychiatry. 1980;13:156-167.
20. Maj, M., Pirozzi, R., Magliano, L. & Bartoli, L. (1998). The long-term result of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients in a lithium clinic. American Journal of Psychiatry, 155, 30 - 35.
21. Maj, M., Pirozzi, R., Formacola, A.M.R., & Tortrella, A. (1999). Reliability and validity of four alternative definitions of bipolar disorder with fast cycling. American Journal of Psychiatry, 158, 303-305.
22. *OECD/EU (2018)*, Health at a Glance: Europe 2018: *State* of Health in the EU Cycle, *OECD Publishing, Paris*. https://doi.org/10.1787/health_glance_eur-2018-en.
23. Psychiatry, 1 and 2 Volume Set 4th Edition. Allan Tasman, Jerald Kay, Jeffrey A. Lieberman, Michael B. First, and Michelle B. Riba, Eds. (2015) Chichester, West Sussex, UK, and Hoboken, NJ. 2684 pages.
24. Sampath H, Sharma I, Dutta S. Treatment of suicidal depression with ketamine in rapid cycling bipolar disorder. Asia Pac Psychiatry. 2016;8(1):98-101.
25. Stanton A Glantz. Primer of biostatistics New York : McGraw-Hill Medical, 2012. 7th ed ISBN-13: 978-0071781503; ISBN-10: 0071781501. 320 pages.
26. The American Psychiatric Association Publishing Textbook of Psychopharmacology fifth edition edited by Alan F. Schatzberg, Charles B. Nemeroff. 2017. 2829 pages.
27. Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. Br J Psychiatry. 2001;178:S184-190. Abstract.
28. Tondo L, Hennen J, Baldessarini RJ. Rapid-cycling bipolar disorder: effects of long-term treatments. Acta Psychiatr Scand 2003; 108:4.
29. Viguera AC, Baldessarini RJ, Tondo L. Response to lithium maintenance treatment in bipolar disorders: comparison of women and men. Bipolar Disord. 2001;3:245-252. Abstract.
30. Stanton A. Glantz. Primer of Biostatistics, 7th Edition,Kindle Edition, 2012, P.298.

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