ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article DOI:10.62425/rtpharma.1614127

A Randomised Controlled Trial to Evaluate Genotyping and Therapeutic Drug Monitoring *vs* Only Therapeutic Drug Monitoring as a Strategy for Risk Minimisation in Epileptic Patients on Carbamazepine Therapy

Mahesh Namdeo BELHEKAR[1]
Vinayak A[1]
Swati MORE[1]
Sanchita AMBRE[1]
Hına KHIMSURIYA[1]
[1]Department of Clinical Pharmacology, First Floor, New MS Building, Seth GSMC and KEMH, Parel, Mumbai, 400012, Maharashtra, India

ABSTRACT

Objective: Carbamazepine (CBZ) is a widely prescribed antiepileptic drug for the treatment of focal seizures. CBZ is metabolised primarily by cytochrome enzymes, particularly CYP3A5. It is difficult to predict clinically whether a patient is likely to suffer from CBZ toxicity. Hence, we aimed to evaluate the use of genotyping and therapeutic drug monitoring (TDM) vs. only TDM in epileptic patients on CBZ as a strategy for risk minimisation.

Methods: This double-blind, randomised controlled trial included 60 patients with epilepsy who were receiving carbamazepine. They were randomly assigned to two equal groups, with one group's carbamazepine dosing guided by genotyping and the other group's doses based solely on clinical judgement.

Results: A total of 60 patients were enrolled in the study and allocated into two groups, group A (both genotyping and TDM) and Group B (only TDM), each arm comprising 30 patients. Among the CYP3A5 metaboliser group, the frequency of expressors and non-expressors was 57% and 43%, respectively. During follow-up visits, at one month, three cases of adverse drug reactions (ADRs) were reported. The number of ADRs decreased to two at the three-month follow-up and declined to a single case at the 12-month assessment. It was found that there is no statistically significant association between CYP3A5 metaboliser and ADR occurrence.

Conclusion: Adding genotyping to TDM did not significantly reduce the risk of carbamazepine toxicity. However, genotyping may still be useful for patients who exhibit symptoms of toxicity.

Keywords: Carbamazepine, Drug Monitoring, Drug-Related Side Effects and Adverse Reactions, Genetic polymorphism, Risk Evaluation and Mitigation

Introduction

Carbamazepine is generally used in patients with generalised tonic-clonic seizures and focal seizures. It is also used for the treatment of bipolar disorders. It shows several "idiosyncratic" adverse effects requiring termination of the therapy (Potter & Ketter, 1993). For the treatment of seizures and bipolar disorders, serum carbamazepine concentrations of 4-12 µg/ml are considered within the accepted therapeutic range (van Tyle & Winter, 2004).

Received 06.01.2025
Accepted 29.04.2025
Publication Date 30.04.2025

Corresponding author: Mahesh Namdeo Belhekar
E-mail: belhekardrmahesh4@gmail.com

Cite this article: Belhekar, M.N., A, V., More, S., Ambre, S. & Khimsuriya, H. (2025). A Randomised Controlled Trial to Evaluate Genotyping and Therapeutic Drug Monitoring vs. Only Therapeutic Drug Monitoring as a Strategy for Risk Minimisation in Epileptic Patients on Carbamazepine Therapy. *Recent Trends in Pharmacology, 3*(1), 27-35.

Pharmacogenetics is the study of the relationship between variations in a single gene and the action of drugs, and these genetic distinctions aid in clarifying the reason for either treatment failure or toxic effects related to several pharmaceutical compounds. It is important to know about these distinctions for the prognosis of the incidence of toxicity amongst patients receiving any drug (Cavalleri et al., 2011). Genetic polymorphisms that occur because of a single-nucleotide exchange in the DNA sequence are more common. Genetic polymorphisms show a significant role in the variability in pharmacokinetics and pharmacodynamics of anti-epileptic drugs (AEDs) and can affect their efficacy, tolerability, safety, and duration of action (Roden, 2006; Seven et al., 2014; Lakhan et al., 2011; Orozco-Suarez, 2014; Franco & Perucca, 2015).

The cytochrome P450 enzymes are involved in the metabolism and elimination of numerous extensively used drugs and are very much predisposed to genetic polymorphism. Carbamazepine elimination is linked to genetic polymorphisms of drug-metabolising enzymes and transporters (Puranik et al., 2013; Yeap et al., 2014). Ninety-nine percent of carbamazepine is metabolised by the liver, and CYP3A4 and CYP3A5 are the most prominent enzymes. Amongst the patients getting the same dose of carbamazepine, it shows a noticeable interindividual distinction in the plasma drug concentrations, which may lead to therapeutic failure or toxicity. It is realised that there are noteworthy inter-individual variances in the expression of CYP3A5, thus showing distinctions in the pharmacokinetics of carbamazepine (Perucca, 2006; Thorn et al., 2011).

Carbamazepine is cleared from the blood at a higher rate of about 8% in patients with CYP3A5*3/*3 alleles as compared to those with CYP3A5*1/*1 or CYP3A5*1/*3 alleles, as reported by Seo et al. (Seo et al., 2006). However, Park et al. (Park et al., 2009) reported that there were higher levels in patients with CYP3A5*3/*3, which were 31% more than those in patients with CYP3A5*1/*1 or CYP3A5*1/*3. Detection of plasma levels is a routine practice that serves as a guide to regulate the titration of doses. It aids in lessening the risk of under- or overdosing due to drug/ food interaction or genetic polymorphism of enzymes and transporters involved in the metabolism of carbamazepine (Raj Panday et al., 2017). A study conducted by Al-Gahtany et. al. (2014) recommended that the CYP3A5 genetic polymorphisms result in toxicity in epileptic patients by playing an important role in the steady-state concentrations of carbamazepine.

Carbamazepine serum disposition is changed by the genetic polymorphisms of metabolic enzymes, necessitating therapeutic dose monitoring. It is almost fully metabolised in the liver, with only approximately 5% of the drug excreted unchanged. Among the diverse types of alleles of CYP3A5, the frequently occurring type, which leads to loss of its function, is the CYP3A5*3 allele. Thus, only people with at least one CYP3A5*1 allele can express large amounts of CYP3A5 (expressors), while individuals homozygous for the mutant allele CYP3A5*3/*3 are considered non-expressors (Milovanovic et al., 2015; Barry & Levine, 2010).

A risk management plan is defined as “a set of pharmacovigilance events and interventions planned to detect, describe, avert or diminish risks relating to medicinal products, including the assessment of the effectiveness of those interventions” (Touw et al., 2005). Carbamazepine produces dose-related neurotoxicity such as sedation, dizziness, vertigo, diplopia, and ataxia. Vomiting, diarrhoea, and worsening of seizures are also seen with higher doses. It can also cause specific rare side effects, including severe cutaneous adverse reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis (Thorn et al., 2011). In addition to adverse events, the absence of efficacy can also be a problem, with as many as 30% of patients with epilepsy facing drug resistance (Sisodiya & Goldstein, 2007).

It is hard to envisage clinically whether a patient is likely to suffer from carbamazepine toxicity. One of the ways to avoid the adverse effects of drugs is through therapeutic drug monitoring (TDM), as it aids in distinguishing between drug toxicity and uninhibited disease for some drugs. TDM aids in speeding up the establishment of a drug regimen for an individual patient. When TDM is performed, the therapeutic ranges that have been established for the drugs in the class should be used only as guides. Genotyping, on the other hand, can aid in personalising carbamazepine therapy by detecting mutations in the enzymes responsible for its metabolism, thus envisaging the dose range for a given drug to circumvent toxicity in the patient. Hence, this study was conducted to compare the addition of genotyping to TDM of carbamazepine as a new tool and assess the plasma levels of carbamazepine as well as the occurrence of ADRs in epileptic patients on carbamazepine therapy as a part of risk minimisation.

Methods

Trial design

The study was a prospective, parallel, double-blind, randomised controlled trial conducted in two groups of epileptic patients on carbamazepine therapy recruited from either the Neurology or Therapeutic Drug Monitoring (TDM) outpatient department (OPD) of a tertiary care teaching hospital in India. It was conducted as per the Indian Council of Medical Research (ICMR) guidelines 2017, and it was approved by the Institutional Ethics Committee [EC/OA-41/2019]. Clinical Trial Registry of India (CTRI) registration was done with the registration number CTRI/2019/09/021311. Written informed consent was obtained from all participants in this study after ethics committee approval. A randomised controlled trial was chosen to compare the efficacy of genotyping-based dosing with standard clinical judgement.

Participants

All patients aged 5 to 85 years, not exposed to carbamazepine therapy in the last year (regardless of monotherapy or polytherapy), were included in the study. Patients with genotyping results (for CYP3A5 polymorphism) known due to prior testing or reports being available in medical records, patients with a history of drug/alcohol abuse, and those with evidence of gastrointestinal tract, renal, endocrine, cardiovascular diseases, etc., and patients with status epilepticus were excluded.

Interventions

After obtaining written informed consent/assent, the patients were randomised into two study arms, with one arm (group A) receiving the therapeutic dose of carbamazepine based on their CYP3A5 genotyping. CYP3A5 expressors (*1/*1 and *1/*3) were given a starting dose of carbamazepine of up to 400 mg twice daily, while CYP3A5 non-expressors (*3/*3) were given a starting dose, as per the neurologist's opinion, up to a maximum dose of 200 mg twice daily. In another study arm (group B), genotyping was not performed initially, and dose administration was based on the clinician's judgement. In both groups, monitoring of carbamazepine levels was performed through TDM. For the patients in group B, genotyping was done after the last follow-up visit to compare the incidence of adverse effects in each group based on their genotypes.

TDM of carbamazepine in both the study arms was done through the estimation of trough levels of carbamazepine concentrations. Trough levels were ensured by educating the patient to visit the OPD before taking the morning dose. Sample collection was done after the completion of 12 hours since the last dosing. Four millilitres (ml) of venous blood samples were collected under aseptic precautions. Samples were centrifuged for the separation of plasma, which was used for estimating the trough levels of plasma carbamazepine using fast elution high-performance liquid chromatography (HPLC) by Chromaster, Japan. Running three-level control sera provided along with the kits ensured maintenance of quality control. These results of carbamazepine TDM level concentrations performed prospectively for one year (1-, 3-, 6- and 12-month follow-up visits) in epileptic patients of either study arm were recorded in case record form (CRF). For DNA extraction and genotyping, the remaining cellular component was stored at −80°C.

Genotyping studies were carried out on these DNA samples after standardising the Polymerase Chain Reaction (PCR) for various parameters such as the DNA and the primer concentrations, dNTPs, $MgCl_2$, and annealing temperature. After optimising the reaction conditions, the DNA samples of the subjects were amplified using primers specific to CYP3A5*3 polymorphisms. The amplified product obtained was then subjected to restriction digestion using a specific restriction enzyme. The product thus obtained was subjected to gel electrophoresis to identify the polymorphism (Adithan et al., 2003; Sullivan-Klose et al., 1996). After obtaining genotyping results in both groups, they were compared with the plasma carbamazepine levels of the participants.

Outcomes

Primary outcome: Comparison of plasma levels of carbamazepine with the CYP3A5 genotype

Secondary outcomes:

- Number of ADRs reported by the study participants
- Comparison of ADRs reported by the participants with their genotype

Sample size

During the planning of the study, there were no similar studies conducted previously. Hence, a convenient sample size of 30 per group was considered.

Randomisation

The randomisation plan was generated from http://www.randomization.com. According to this plan, the patients were divided into two blocks of randomisation with an allocation ratio of 1:1. Allocation concealment was done using opaque, sealed envelopes.

Blinding

Both the patients and the observer (junior clinician) were blinded to the intervention received. The observer assessed only the primary outcome measure of estimating plasma levels of carbamazepine. Another observer (senior clinician) was unblinded to the intervention, noted the ADRs in case they occurred in any of the patients and initiated and appropriately titrated the carbamazepine doses.

Statistical methods

The baseline demographic data were summarised using descriptive statistics. Plasma levels of carbamazepine and ADRs were recorded as categorical data and were summarised as frequencies and percentages. The difference between the two study arms regarding the occurrence of ADRs was analysed using the Chi-Squared test. All analyses were done at 5% significance.

Results

The study period was planned to be completed over two years, but was extended due to the COVID-19 pandemic. 60 patients were enrolled in the study, and all of them completed it as shown in Figure 1.

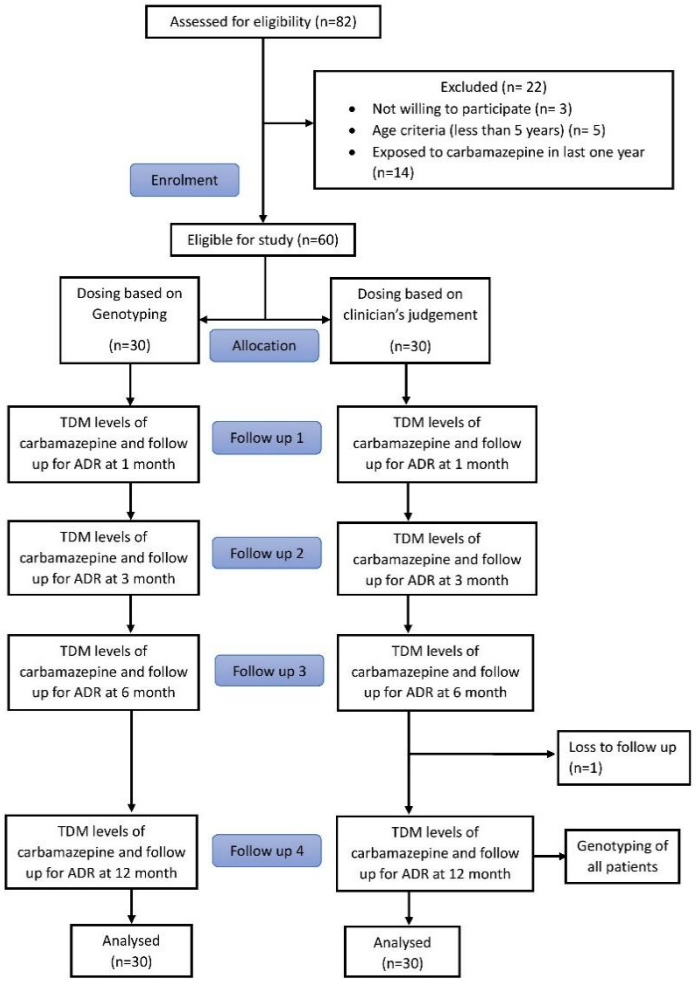

Figure 1. CONSORT flow chart

The baseline characteristics are given in Table 1.

Table 1: Baseline characteristics of study participants

Characteristics		Group A	Group B	*P*
Age (years)		23.21 ± 10.44	24.45 ± 11.44	.67$
Sex	**Male**	12	19	.07#
	Female	18	11	
Weight (kg)		50.66 ± 15.88	55.04 ± 18.10	.33$
Baseline plasma carbamazepine levels (µg/ml)		0.604 ± 0.566	0.433 ± 0.375	.18$

*P*s calculated using unpaired t-test$ and chi-squared test#

Among the CYP3A5 metaboliser group, the frequency of expressors and non-expressors was 34 (56.7%) and 26 (43.3%), respectively. The difference in the mean age of

patients on carbamazepine therapy among CYP3A5 expressors and non-expressors is statistically not significant. To assess the association of CYP3A5 metaboliser status with gender, a chi-square test was used, which indicated that there was no statistically significant association, as depicted in Table 2. Uncontrolled seizures, suspected non-compliance and features of toxicity were the main indications for carrying out TDM in these patients.

Table 2: Difference in gender among CYP3A5 expressors and non-expressors

CYP3A5 metaboliser			
Gender	**Expressers n (%)**	**Non-expressers n (%)**	***P***
Female	15 (51.7)	14 (48.3)	.46
Male	19 (61.3)	12 (38.7)	

P calculated using chi-square test

Table 3 shows the plasma carbamazepine levels over the entire study period.

Table 3: Plasma carbamazepine levels over the entire study period

Follow-up visit (months)	**Group A**	**Group B**	***P***
1	4.602 ± 2.326	4.637 ± 2.274	.95
3	5.604 ± 2.441	5.02 ± 1.468	.28
6	5.13 ± 1.619	5.148 ± 1.125	.96
12	5.432 ± 1.524	5.019 ± 0.898	.22

P calculated using an unpaired t-test

Table 4 shows the association of CYP3A5 metaboliser with the plasma levels of carbamazepine at one, three, six, and 12-month follow-up periods. The results indicate that CYP3A5 metaboliser status was not significantly associated with the plasma levels of carbamazepine during the follow-up periods.

Table 4: TDM levels in CYP3A5 expressors and non-expressors

CYP3A5 metaboliser			
	Expressors n (%)	**Non-expressors n (%)**	***p***
Plasma level of carbamazepine (1-month follow-up) [below/within/above laboratory reference range]			
Below	15 (53.6)	13 (46.4)	.65
Within	19 (59.4)	13 (40.6)	
Plasma level of carbamazepine (3 months follow-up) [below/within/above laboratory reference range]			
Below	8 (66.7)	4 (33.3)	.38
Within	25 (53.2)	22 (46.8)	
Above	1 (100)	0	
Plasma level of carbamazepine (6-month follow-up) [below/within/above laboratory reference range]			
Below	5 (45.5)	6 (54.5)	.51
Within	29 (59.2)	20 (40.8)	
Plasma level of carbamazepine (12-month follow-up) [below/within/above laboratory reference range]			
Below	2 (33.3)	4 (66.7)	.39
Within	32 (59.3)	22 (40.7)	

TDM: Therapeutic Drug Monitoring
*P*s calculated using the chi-square test

During the follow-up visits, at the one-month follow-up period, three cases of ADRs were reported. The ADR count decreased to two cases during the three-month follow-up and decreased to only one case of ADR at the 12-month assessment. These results are shown in Table 5.

Table 5: Number of ADR occurrences in each group

Follow-up visit (months)	**Group A**	**Group B**	***P***
1	2	1	.39
3	1	1	
6	0	0	
12	0	1	

ADR: Adverse Drug Reaction
P calculated using Fischer's exact test

Assessment of the association of CYP3A5 metaboliser status of carbamazepine and ADR indicated that there was no statistically significant association, as depicted in Table 6 below.

Table 6: Occurrence of ADRs in CYP3A5 expressor and non-expressor groups

CYP3A5 metaboliser			
	Expressers n (%)	**Non-expressers n (%)**	***p***
Occurrence of ADR (1-month follow-up)			
No	31 (54.4)	26 (45.6)	.25
Yes	3 (100)	0 (0)	
Occurrence of ADR (3-month follow-up)			
No	32 (55.2)	26 (44.8)	.50
Yes	2 (100)	0 (0)	
Occurrence of ADR (12-month follow-up)			
No	34 (57.6)	25 (42.4)	.43
Yes	0 (0)	1 (100)	

ADR: Adverse Drug Reaction

*P*s calculated using the chi-square test

Discussion

This is the first study conducted on Indian epileptic patients on carbamazepine therapy to find out the utility of TDM and genotyping in risk minimisation. This study will contribute to the literature by providing an improved understanding of CYP3A5 polymorphisms in epilepsy patients on treatment with carbamazepine. Earlier research, including studies from Asian countries such as Japan (Seo et al., 2006), Korea (Park et al., 2009), China (Meng et al., 2011; Lu et al., 2018), and Thailand (Panomvana et al., 2013), studied the association between the CYP3A5 genotypes and the disposition of carbamazepine (Thorn et al., 2011). Whereas this association remains indecisive, no such randomised controlled trial has been conducted in Indian epileptic populations.

In our study, the mean age of patients was 24 years, with a male preponderance. The findings of our study were consistent with the mean age of patients in a study done by Ganesapandian et. al. (2019) in the South Indian population. In our study, we found that among male patients on carbamazepine therapy, 61% were expressors and 39% were non-expressors of CYP3A5, while in the study conducted by Ganesapandian et. al. (2019), they found 45% expressers and 55% non-expressors of CYP3A5 among male patients on carbamazepine therapy. In the case of female patients, we found 52% were expressors and 48% were non-expressors of CYP3A5, while in the same study conducted by Ganesapandian et. al. (2019), they found 55% expressers and 45% non-expressors among female patients. A similar pattern of CYP3A5 expression among both genders in both studies was observed.

In our study, the mean baseline carbamazepine plasma levels at the time of patient enrollment were 0.52 µg/ml, well below the laboratory reference range of 4-12 µg/ml, confirming that the patients had received no treatment. During a monthly follow-up period of patients, we found that the mean plasma carbamazepine levels were within the laboratory reference range in 53% (both arms of patients) after starting carbamazepine therapy. Though the mean plasma levels appeared to be within the laboratory reference range at one-month follow-up, only 59% of expressors and 41% of non-expressors had plasma levels within the laboratory reference range. This may be because carbamazepine, being an effective enzyme inducer, causes autoinduction by stimulating CYP3A4, and it is usually completed within 3–5 weeks (Pynnönen et al., 1980).

In our study during the follow-up period, only one patient on carbamazepine (out of 60 patients enrolled) had plasma levels above the laboratory reference range at three three-month follow-up visits, and he was a CYP3A5 expressor. Nevertheless, it is well known that increased plasma concentration of carbamazepine is detected in non-expressers. The explanation for this is that the CYP3A5*3 allele has a guanine (G) nucleotide instead of an adenosine (A), creating a cryptic splice site in intron 3 and changing the mRNA splicing. This causes early termination of protein synthesis, leading to the production of nonfunctional proteins. Patients with a homozygous genotype of CYP3A5*3/*3 thus create a nonfunctional enzyme (Kuehl et al., 2001) and end up poorly metabolising carbamazepine.

Our study results showed no statistically significant association of CYP3A5 metaboliser status with the plasma levels of carbamazepine at one, three, six, and 12-month follow-up periods. These results are similar to Panomvana et al. (2013), who studied the effect of CYP3A5 genotypes on carbamazepine levels and clearance in the Thai population. This study was conducted in epileptic patients on carbamazepine monotherapy as well as in patients on carbamazepine with other antiepileptic drugs, such as phenytoin, phenobarbitone, and valproate. They found no significant difference in dose-adjusted carbamazepine levels among expressors and non-expressors. This could be due to the insufficient sample size of 36 patients on carbamazepine monotherapy.

In our study, the number of patients who presented

with ADRs was the same (n=3) in both the study arms. The ADRs occurred in [5 out of 34 (15%)] patients who were CYP3A5 expressors and [1 out of 26 (4%)] patients who were CYP3A5 non-expressors. This finding is in contrast with the study conducted by Ganesapandian et. al. (Ganesapandian et al., 2019) where 16 % of ADRs were found among expressors and 35% of ADRs were found among non-expressors. The clinical carbamazepine toxicity in our study consisted of drowsiness (n=3), giddiness (n = 1), headache (n =1), and weight gain (n = 1). Among these, the patient with giddiness was a CYP3A5 expressor and had plasma levels above the laboratory reference range, and another patient with drowsiness, who was also a CYP3A5 expressor, had plasma levels below the laboratory reference range.

We have conducted this study as a vital step in the combination of pharmacogenetics and TDM to know the determinants of carbamazepine risk minimisation. There are differing results on the effect of the CYP3A5 genotype on carbamazepine levels, and hence, there is a necessity for efficacy guidelines for the genotype-based dosing of carbamazepine along with existing Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for HLA genotype.

Limitations

One of the limitations of our study was the small number of participants. Our study genotyped only CYP3A5, while another isoform may play an important role in the metabolism of carbamazepine.

Conclusion and Recommendations

It is concluded that there is no significant usefulness of the addition of genotyping in risk minimisation of carbamazepine when used with TDM. Genotyping can be considered only in those patients on carbamazepine with symptoms of toxicity. The Polymerase Chain Reaction (PCR) - Restriction Fragment Length Polymorphism (RFLP) technology for genotyping of carbamazepine [as CYP3A5 genotype - expressors or non-expressors] method will eventually be used for routine patient care in a public sector tertiary care teaching hospital in India.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Ethics Committee-1 of Seth G.S. Medical College and K.E.M. Hospital, Mumbai (Date: August 23, 2019, Project Number: EC/OA-41/2019).

Informed Consent:

1. I have read or have had read to me the information given in the Informed Consent Document for this study entitled "A randomized controlled trial to evaluate genotyping and therapeutic drug monitoring vs. only therapeutic drug monitoring as a strategy for risk minimization in epileptic patients on carbamazepine therapy."
2. I have received an explanation of the nature, purpose, duration, and foreseeable effects and risks of the trial and what I will be expected to do. My questions have been answered satisfactorily.
3. I understand that my participation in the study is voluntary and that I may refuse to participate or may withdraw from the study at any time, without penalty or loss of benefits to which I am otherwise entitled.
4. I further understand that any information that becomes available during the course of the study that may affect my willingness to take part will be informed to me.
5. I give permission to allow the study personnel to withdraw my blood (4.0 ml) for the determination of plasma carbamazepine levels and genotyping.
6. Institutional ethics committee authorities may wish to examine my medical records to verify the information collected. By signing/giving a thumb impression on this document, I give permission for this review of my records.
7. I understand that my identity will not be revealed in any report or publication.
8. I agree to take part in the above study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept -MB; Design-MB; Supervision-MB; Resources-MB, VA; Data Collection and/or Processing-MB, SM, SA, HK; Analysis and/or Interpretation-VA; Literature Search-MB, VA; Writing Manuscript-MB, VA, SM, SA, HK; Critical Review-MB; Other-Nil

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study was funded by Seth G S Medical College Multidisciplinary Research Unit, Mumbai, under centrally sponsored scheme of Department of Health Research, Government of India No: V.25011/85/2014-MRU/HR dated 22.09.2014

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