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Factors Influencing Plasma Concentrations of Phenytoin, Phenobarbitone, Carbamazepine and Sodium Valproate in Epileptic Patients Attending a Tertiary Care Hospital

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ABSTRACT

Objective: The traditional anti-epileptic drugs like phenytoin, sodium valproate and carbamazepine continue to be used widely in the low to middle income countries due to their time tested efficacy and low costs. The factors which affect the AED concentrations in non-toxicity indications has not been reported so far. Hence, we studied the factors that could influence the plasma concentrations of these AEDs. **Methods:** This is a retrospective record based study and a short term prosepective study. Requisition forms of epileptic patients referred for TDM 2012-2014 were compared with the AED concentrations reported. Epileptic patients who were referred during May-June 2015 for TDM were evaluated for their seizure history and anthropometic measurements for calculation of extracellular volume (V_{ECW}) and compared with the AED concentrations. **Results:** Out of the 170 requisitions for TDM, 68.2% were monotherapy and 31.8% received two or more antiepileptic drugs. In 44% of patients, the plasma concentrations of the AED correlated with clinical response. In our study the plasma level of carbamazepine was found to be reduced by phenytoin, sodium valproate concentration was reduced by carbamazepine and phenytoin levels were reduced by sodium valproate. In male, phenytoin levels were significantly lower than in female, Phenytoin decreased carbamazepine levels significantly in female. Carbamazepine significantly decreased sodium valproate concentrations in females. Carbamazepine dose adjusted for weight and V_{ECW} was found to show a trend of correlation to the blood levels, **Conclusion:** TDM for AEDs is an indispensable investigation that guides the clinicians to tailor dose of drugs in individual patients. Factors such as age, gender, concomitant drugs in general and V_{ECW} in patients on carbamazepine needs to be considered while interpreting AED plasma concentrations for monitoring therapy.

Key words: Antiepileptics, Therapeutic drug monitoring, Phenytoin, Carbamazepine, Sodium valproate.

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INTRODUCTION

Traditional Antiepileptic Drugs (AED) namely phenytoin, phenobarbitone, carbamazepine and sodium valproate are commonly prescribed for the management of tonic-clonic, partial, or absence seizures either as monotherapy or polytherapy owing to their time tested efficacy and lower costs. As these drugs have a narrow therapeutic index and due to the inter-individual pharmacokinetic variations, Therapeutic Drug Monitoring (TDM) is used to optimize pharmacotherapy in individual epileptic patients.

TDM helps to optimize the dose of AED during initiation, maintenance of therapy as well during the occurrence of toxicity.[1] The usefulness of measuring plasma concentrations of AEDs lies in choosing the appropriate epileptic patients with clear indications for TDM and also interpreting the results critically while correlating with clinical improvement.

The therapeutic level of phenytoin is 10-20 mcg/ml, phenobarbitone is 10-40 mcg/ml, carbamazepine is 4-12 mcg/ml and sodium valproate is 50-100 mcg/ ml as recommended by International League against Epilepsy (ILAE).[2] However, it is reported that patients having plasma concentrations within therapeutic range show clinical symptoms of toxicity.[3]

The plasma concentration of AEDs can be influenced by many factors like age, gender, duration of epileptic disorder, drug interactions with concomitant drugs, compliance, co-morbid conditions of the patient as well as the genetic make-up of the individual.[4-6] Phenytoin, phenobarbitone and carbamazepine are inducers of cytochrome enzymes and sodium valproate is an inhibitor of these enzymes.[7] When a patient receives a combination of these drugs, the interactions can reduce the effect of drug therapy and/or can cause adverse effects. TDM helps to determine the dose of individual drugs that are needed to optimize therapy.

The relationship between the dosing and plasma levels of AEDs is uncertain. Studies have shown that daily dose of carbamazepine and phenobarbitone expressed in terms of extracellular water volume was found to correlate better with their serum concentrations.[8,9] Other studies reported from India have found that in many patients, the plasma levels do not correlate with the clinical response.[10]

Studies discussing the effects of combination therapy on the plasma concentrations of carbamazepine, phenytoin and sodium valproate found that carbamazepine and phenytoin decreased the levels of concomitantly administered drugs.[2,6] Conflicting reports exist about whether or not Sodium Valproate significantly elevates the levels of concomitant drugs.[6,11] Differences in plasma levels between genders in certain combination therapies of AEDs have been found,[2] but their effect on therapeutic outcome is uncertain.

Though used widely in developing countries as well as to some extent in developed countries, very few studies have analysed the influence of demographic and other factors in determining the plasma levels of the traditional antiepileptics.

Aim: We wanted to analyse the TDM reports of AEDs for their correlation with standard values as well as the clinical indication. In addition, we wished to analyse the effect of factors like age, gender, weight, extracellular body water volume (V_{ECW}) and anti-epileptic drug combinations on the plasma levels of the four antiepileptic drugs.

Ethics approval: The Institute Ethics Committee approved the protocol and waiver of consent for the retrospective study was granted. For the prospective study, a written informed consent was obtained from all participants before recruitment.

MATERIALS AND METHODS

This was a prospective and retrospective record based study design involving epileptic patients referred for TDM of AED to the Pharmacology department of JIPMER during 2012-2014 and epileptic patients who were referred during May-August 2015 for TDM.

For the Retrospective Study, **r**equisition forms of patients between 18-65 years of age who underwent TDM during 2012-2014 and which had details of age, gender, body weight and the indication for TDM were included for the study. Requistion forms without complete information, patients without an epileptic disorder and patients referred for toxicity confirmation were excluded from the study.

For the prospective study, all epileptic patients 18-65 years of age who were referred for TDM of AEDs, patients taking AEDs for a period more than 3 months, history of good compliance to intake of AEDs as told by the patient and/or the accompanying relative were included and patients without an epileptic disorder , with known liver or renal dysfunction during sample collection for TDM, history of any concomitant chronic diseases like hypertension, diabetes for which patient was receiving medications were excluded.

Data collection for the retrospective study

For the retrospective study, all requisition forms for TDM of AEDs during the year 2012-2014 which satisfied the inclusion-exclusion criteria were collected from the TDM lab of pharmacology department. Patient identity, age, body weight, AED and other drug details including the dose, indication and AED(s) for TDM and concomitant drugs administered were noted down. The TDM reports against these requisitions were collected from the registers for this period and the plasma concentrations of the AED were utilized for analysis.

Data collection for the prospective study

For the prospective study, all epileptic patients referred for TDM during the four months of May to August 2015 were included based on the inclusion and exclusion criteria. Written informed consent was obtained and all procedures were according to the ethical standards of Helsinki declaration. The details (patient age, body weight, AED and other drug details including the dose, indication and AED(s) for TDM and concomitant drugs) were noted down from the requisition forms and height of the patient was recorded in order to calculate the ECW. Compliance was checked by asking the patient and the caretaker accompanying the patient for regular intake of AED for the past 3 months. Frequency of seizures in the last 12 months as well as in the pre-intervention period was checked from the case records and by asking the patient. Five ml of blood was collected for TDM estimation as a routine procedure. TDM for Phenytoin, Phenobarbitone, Carbamazepine and/or Sodium Valproate as per the requisition of the clinician was done by High Performance Liquid Chromatography (HPLC) method which is standardized and performed for routine patient care.

V_{ECW} was calculated using the formula:[8]

$$V_{ECW} = 0.068 \times \text{body weight [kg]}^{0.40} \times \text{height[cm]}^{0.633}$$

Clinical response was assessed as per the International League Against Epilepsy Guidelines[2] and was classified into either Category 1 Outcome (Seizure Freedom), Category 2 Outcome (Treatment Failure), or Category 3 Outcome (Undetermined). Seizure Freedom is defined as freedom from seizures for a minimum of three times the longest pre-intervention inter-seizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer. On the other hand, treatment failure (Category 2 outcome) is defined as recurrent seizure(s) after the intervention has been adequately applied. If a patient had been seizure free for three times the pre intervention inter-seizure interval but for <12 months, seizure control was be "undetermined". However, if the patient experiences another seizure before the end of 12 months, treatment was marked as "failed".

Statistical analysis

The TDM reports on plasma AED levels were expressed as concentrations and mean±SD. For statistical analysis, we used Instat GraphPad v3.02 and IBM SPSS v20. We calculated the Extracellular Water Volume (V_{ECW}) and we did a regression analysis between Daily Dose/V_{ECW} and the plasma concentration of the drug.

For the retrospective study

We classified the patients based on whether they were receiving monotherapy or combination therapy of AEDs. We then further classified them based on their plasma concentrations and indication for TDM request.

Average plasma levels of AED for patients on monotherapy and combination therapy was calculated. The difference in plasma levels of a drug between monotherapy and combination therapy was analysed for significance.

Average plasma levels of AEDs were calculated gender-wise for patients on monotherapy and combination therapy. The difference in plasma levels between similar combinations between genders was analysed for significance.

Finally, plasma concentration of drug was correlated with age, gender and dose per day of drug using linear regression analysis.

For the prospective study

The Dose/V_{ECW} was calculated and its correlation with plasma level of the drug was analysed using linear regression analysis.

RESULTS

Retrospective study

There were 480 requisitions for TDM of AEDs in the period between 2012-2014 for epileptic indications. The total number of patients in this period that fit the inclusion and exclusion criteria was 170. Out of this, the number of males were 89(52.35%) and the number of females were 81(47.65%). The number of patients receiving Phenytoin monotherapy was 50; Phenobarbitone monotherapy one; Carbamazepine monotherapy 47; and Sodium Valproate monotherapy 18. Among the patients receiving combination therapy of two drugs, phenytoin-sodium Valproate was the highest with 16 patients, followed by carbamazepine-sodium Valproate with 14 (Table 1). Four patients received a combination therapy of three drugs, out of which three patients received phenobarbitone-carbamazepine-sodium valproate combination and one received phenytoin-sodium valproate-carbamazepine combination.

Table 1: Distribution of various AED combinations in Patients referred for non-toxicity indications.

Drug	Alone	+PHEN	+CBZ	+VPA	+PHB
Carbamazepine	47	7	-	14	10
Phenytoin	50	-	7	16	2
Sodium Valproate	18	16	14	-	1
Phenobarbitone	1	2	10	1	-

AED- Anti-Epileptic Drugs; +PHEN- In addition to phenytoin, +CBZ- In addition to carbamazepine, +PHB- In addition to phenobarbitone, +VPA-In addition to sodium valproate

Table 2: Distribution of patients on AED monotherapy based on indication for TDM between 2012-14.

Indication	Phenytoin(50)		Phenobarbitone(1)		Carbamazepine(47)		Sodium Valproate(18)	
	TH*	NTH¶	TH	NTH	TH	NTH	TH	NTH
Routine	0	8(16%)	0	0	3(6%)	3(6%)	1(5.5%)	1(5.5%)
Failure of therapy	9(18%)	33(66%)	0	1(100%)	32(68%)	9(20%)	6(33.3%)	10(55.7%)

*TH-Therapeutic Range, ¶NTH-Non-Therapeutic range.

Table 3: Average*concentrations of AEDs (mcg/ml) in monotherapy and two drug combination therapy.

Drug	Alone	+PHEN	+CBZ	+PHB	VPA
Carbamazepine	6.03±3.24	4.63±2.40	-	8.26±7.52	3.36±2.19$
Phenytoin	8.68±7.86	-	3.18±1.62$	10.75±7.85	5.92±3.99
Sodium Valproate	185.11±208.19	93.60±96.66$	89.44±75.28	108.00±0.00	-
Phenobarbitone	6.00±0.00	6.85±9.69	12.68±9.30	-	5.30±0.00

*Average expressed as Mean ± Standard Deviation, AED- Anti-Epileptic Drugs; +PHEN- In addition to Phenytoin, +CBZ- In addition to Carbamazepine, +PHB- In addition to Phenobarbitone, +VPA-In addition to Sodium Valproate; $- $p<0.05$

For the patients on monotherapy of AED, there were 16 TDM requests for "Routine Analysis" and 97 TDM requests for "Failure of therapy". This distribution of AED drug levels in patients to fall within and out of the standard therapeutic range is shown in Table 2. In 44% of cases, the drug levels were found to be in the therapeutic range.

The average daily dosing of phenytoin, phenobarbitone, carbamazepine and sodium valproate were 277.33 mg, 86.47 mg, 922.56 mg and 822.74 mg respectively. Except for phenytoin, all other drugs fall within the range of recommended therapeutic dose for maintenence therapy.

The average plasma concentrations of the AEDs in monotherapy and in two drug combination therapy are expressed in Table 3.

The average plasma concentration of Phenytoin in monotherapy was 8.68 mcg/ml. In combination with Carbamazepine, the concentration of phenytoin fell to 3.18 mcg/ml and it was statistically significant (p=0.023). There was no significant difference in the concentrations of phenytoin in monotherapy and in combination with sodium valproate.

The average plasma concentration of carbamazepine in monotherapy was 6.03 mcg/ml. In combination with sodium valproate, the concentration of carbamazepine fell to 3.36 mcg/ml and it was statistically significant (p=0.079). There was no significant difference in the concentrations of carbamazepine in monotherapy and in combination with phenytoin.

The average plasma concentration of sodium valproate in monotherapy was 185.11 mcg/ml. In combination with Phenytoin, the concentration of sodium valproate fell to 93.60 mcg/ml and it was statistically significant (p=0.03). There was no significant difference in the concentrations of sodium valproate in monotherapy and in combination with carbamazepine.

Gender-wise distribution

The average plasma concentration of phenytoin in females receiving monotherapy was 6.81 mcg/ml and in males receiving phenytoin monotherapy was 10.15 mcg/ml. This difference is statistically significant (p=0.0146). In women, the difference in levels of phenytoin in phenytoin monotherapy vs phenytoin-carbamazepine combination therapy is significant (p=0.036). In men, the difference in levels of phenytoin in phenytoin monotherapy vs phenytoin-valproate combination is significant (p=0.0288). The difference in other similar drug therapies of phenytoin between genders is not statistically significant. The gender-drug combination distribution of phenytoin levels is given in Figure 1.

In men, the difference in levels of carbamazepine in carbamazepine monotherapy vs carbamazepine- sodium valproate combination was significant (p=0.0233). The difference in similar drug therapies of carbamazepine between genders is not statistically significant. The gender-drug combination distribution of carbamazepine levels is given in Figure 2.

In women, the difference in levels of sodium valproate in sodium valproate monotherapy vs sodium valproate -carbamazepine combination is significant (p=0.0262). The difference in similar drug therapies of sodium valproate between genders is not statistically significant. The gender-drug combination distribution of sodium valproate levels is given in Figure 3.

Further, we did a regression analysis with the dependent variable as plasma drug concentration; and the independent variables being age, gender and dose per day of the drug for all four AEDs separately. However, no

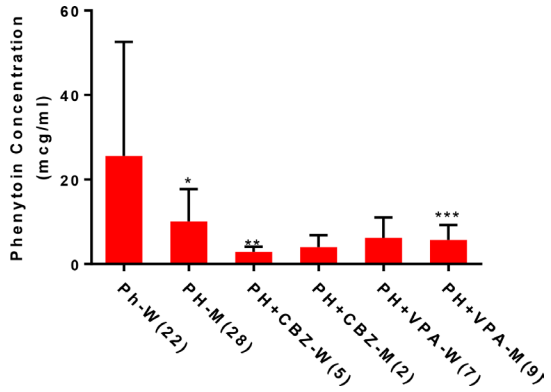

Figure 1: The average plasma concentrations of phenytoin in male and females treated with Phenytoin monotherapy and combination therapy. Ph-W: Female patients treated with Phenytoin Alone; PH-M: Male patients treated with Phenytoin alone; PH+CBZ-W: Female patients treated with Phenytoin-Carbamazepine combination; PH+CBZ-M: Male patients treated with Phenytoin-Carbamazepine combination; PH+VPA-W: Female patients treated with Phenytoin-Sodium Valproate combination; PH+VPA-M: Male patients treated with Phenytoin-Sodium Valproate combination. Numbers in parenthesis denote size of the sample. *-Different from Ph-W; **-Different from Ph-W; ***-Different from Ph-M

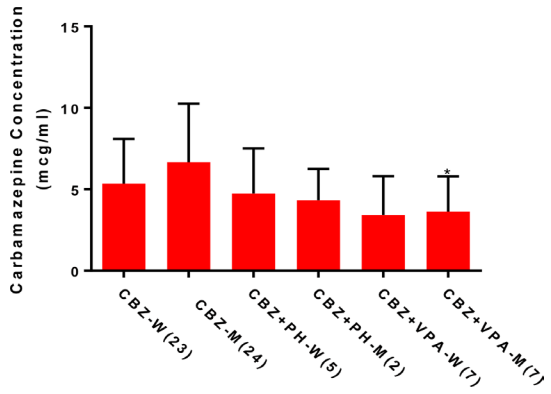

Figure 2: The average plasma concentrations of Carbamazepine in males and females treated with Carbamazepine monotherapy and combination therapy. CBZ-W: Female patients treated with Carbamazepine Alone; CBZ-M: Male patients treated with Carbamazepine alone; CBZ+PH-W: Female patients treated with Carbamazepine-Phenytoin combination; CBZ+PH-M: Male patients treated with Carbamazepine-Phenytoin combination; CBZ+VPA-W: Female patients treated with Carbamazepine -Sodium Valproate combination; CBZ+VPA-M: Male patients treated with Carbamazepine-Sodium Valproate combination. Numbers in parenthesis denote size of the sample. *-Different from CBZ-M.

significant result was attained for any of the four regression analyses (p>0.05).

Prospective study

In the prospective study, a total of 42 patients (20 male and 22 female) who met the inclusion criteria were included. Among the recruited patients, 22 were on carbamazepine, 13 on sodium valproate, 22 on phenytoin either as monotherapy or combination therapy. There was a theoretically positive correlation between the carbamazepine blood levels and body weight adjusted daily dose (p=0.02). Similarly a positive correlation was found between carbamazepine blood levels and V_{ECW} adjusted daily dose (p=0.03) though not appreciable in the graph (Figure 4).

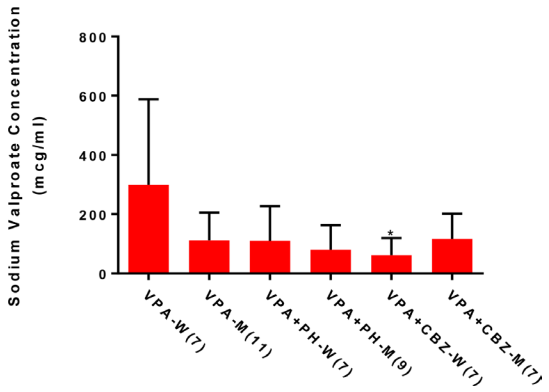

Figure 3: The average plasma concentrations of Sodium Valproate in males and females treated with Sodium Valproate monotherapy and combination therapy. VPA-W: Female patients treated with Sodium Valproate Alone; VPA-M: Male patients treated with Sodium Valproate alone; VPA+PH-W: Female patients treated with Sodium Valproate-Phenytoin combination; VPA+PH-M: Male patients treated with Sodium Valproate-Phenytoin combination; VPA+CBZ-W: Female patients treated with Sodium Valproate-Carbamazepine combination; VPA+CBZ-M: Male patients treated with Sodium Valproate-Carbamazepine combination. Numbers in parenthesis denote size of the sample. *-Different from VPA-W.

Therapeutic drug monitoring is commonly practiced to estimate plasma levels and thus guide the pharmacotherapy of antiepileptic drugs in clinical practice.

DISCUSSION

In our retrospective study, out of the 170 requisitions for TDM 68.2% were monotherapy and 31.8% received two or more antiepileptic drugs. A greater proportion of patients received monotherapy as it is known that majority of the patients can be controlled by a single antiepileptic agent early in the disease process. Monotherapy is also preferred due to decreased instances of drug-drug interactions and adverse drug reaction. In the studies reported earlier, about 7-33 % of the epileptic patients received more than a single antiepileptic drug simultaneously.[4,7,10]

In our study, the average plasma concentration of phenytoin, carbamazepine, phenobarbitone and sodium valproate were 8.68±79, 6.03±3.24, 6.00±0 and 185.12±21 mcg/ml respectively in patients receiving monotherapy, 44 % of samples found to be in the therapeutic range. The plasma concentration values were within the therapeutic range for carbamazepine, below the therapeutic range for phenytoin and phenobarbitone and well above the range for sodium valproate. This is due to the fact that these values represent both routine therapy and failure of therapy. Sirmagul *et al*. has reported average plasma concentrations of carbamazepine as 3.39±0.27 and sodium valproate as 44.44 ± 2.51 mcg/ml, both below the therapeutic range.[4]

There were only 17 patients who were on phenobarbitone therapy and hence it was excluded for analysis of combination therapy.

The plasma level of carbamazepine was found to be reduced by phenytoin in our study, sodium valproate concentration was reduced by carbamazepine and phenytoin levels were reduced by sodium valproate. It is known that phenytoin and carbamazepine are enzyme inducers. Phenytoin can decrease the concentration of other antiepileptic drugs by inducing CYP3A4, CYP2C9, CYP2C19 and CYP1A2 enzymes in the liver and accelerating their metabolism. Sodium valproate is known to be an enzyme inhibitor and hence it increases the levels of co-administered drugs.[2,5] In our study, a significant decrease in carbamazepine concentration was seen on adding sodium valproate only in women. This is similar

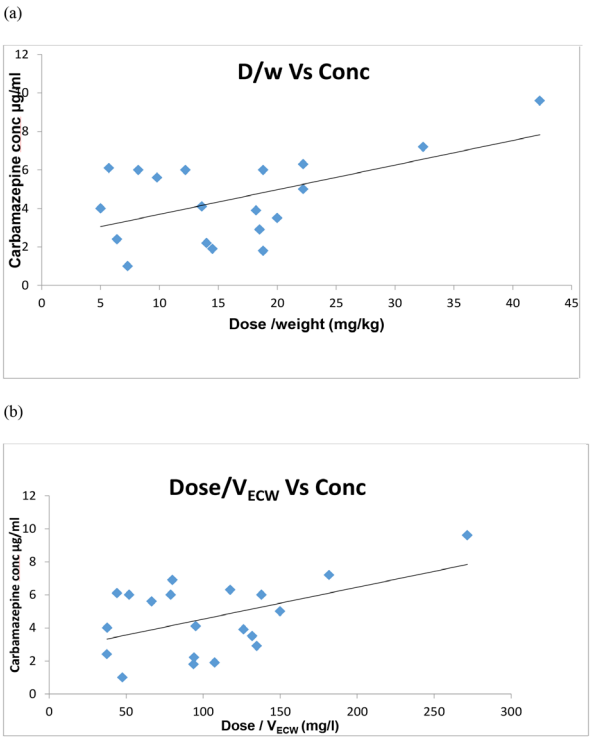

Figure 4: Relation between CBZ concentration and (a) daily dose per weight (r^2 – 0.24, p= 0.02) and (b) daily dose per V^{ECW} (r^2 – 0.24, p= 0.03).

to a study where sodium valproate was shown not to have a significant change in carbamazepine levels.[11]

In males, phenytoin levels were significantly lower than in females, similar to the study by Sirmagul *et al*. This could be due to the fact that the levels of CYP2C9 and CYP2C19 that metabolise phenytoin are higher in males.[11-13] Phenytoin decreased carbamazepine levels significantly in females. Carbamazepine significantly decreased sodium valproate concentrations in females which could be due to higher sensitivity of cytochrome enzymes in females. Gender is therefore an important factor that affects antiepileptic drug pharmacokinetics.[14]

Most patients in the study belonged to the age group between 24-35 years and hence age was not considered as a factor to influence plasma levels in the analysis.

For the prospective study, though some correlation was found for dose adjusted for weight and V_{ECW} with carbamazepine blood levels, a larger sample size could have given a better association profile of the effect of D/V_{ECW} on plasma concentrations of AEDs. However, V_{ECW} has shown to be a good transforming factor to calculate plasma concentrations of AEDs.[8,9] Future studies with a larger sample size may be helpful in evaluating this factor.

CONCLUSION

Plasma concentrations of AEDs in non-toxicity indications fall within ILAE reference range only in 44% cases. Gender, concomitant AEDs, dose of drug corrected for weight and V_{ECW} could influence the plasma levels. The correlation of AED levels with weight and V_{ECW} needs to be explored with a larger sample size.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AED: Anti-Epileptic D; **ILAE:** International League against Epilepsy; **TDM:** Therapeutic Drug Monitoring.

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