

The effect of Valproate, Levetiracetam, and Oxcarbazepine monotherapy on thyroid function in epileptic children**Manish Ajmariya^a, Deepak Sinha^a, Puneet Agrawal^a, Abhishek Mehta^{b*}, Deepika Singh^a**

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Abstract

Background: Epilepsy is a widespread neurological illness with significant medical, social, and psychological implications. Valproate, Oxcarbazepine, and Levetiracetam are the most regularly used long-term antiepileptic drugs (AEDs) in children today.

Objectives: To assess the effect of Valproate, Levetiracetam, and Oxcarbazepine monotherapy on thyroid function of children with epilepsy.

Patients and methods: This prospective observational study was carried out from May 2019 to December 2020 involving children of age group 1-12 years. Any child with newly diagnosed epilepsy being started on monotherapy with Levetiracetam/Valproate/Oxcarbazepine was included in the study. Their baseline thyroid profile and thyroid function at 6th month and 12th month of starting the antiepileptics were evaluated through Biochemical parameters -T3, T4 & TSH. These values were analyzed and compared by applying paired t-test to determine the effect of antiepileptic therapy on the thyroid function of the study subjects.

Results: In the study, a total of 66 study participants were included of which 51 (77.3%) were males and 15 (22.7%) females. Among the study participants, generalized tonic-clonic seizures were seen in 36 (55%) study participants. As an antiepileptic treatment, Valproate was administered to 34 (51.5%), levetiracetam to 24 (36.4%), and oxcarbazepine to 8 (12.1%) of the study participants. Mean values of TSH, total T3, and total T4 scores at baseline were 1.7, 3.04, and 8.05 respectively; at 6 months were 3.17, 3.4, and 1.4 respectively, at 12 months were 4.9, 3.2, and 5.9. A significant increase in TSH and decrease in T4 values as compared to baseline levels was observed after antiepileptic therapy in the target group indicating a suppressive effect on thyroid function.

Conclusion: This study has depicted a significant negative effect of anti-epileptic therapy on thyroid function in children.

Keywords: Epilepsy, Children, Antiepileptic drugs, Thyroid function

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Introduction

Epilepsy is one of the most common neurological disorders having important medical, social, and psychological consequences.

As per the latest stand of the International League Against Epilepsy (ILAE), a person is considered to have epilepsy if he/she meets any of the following criteria:

- At least two unprovoked (or reflex) seizures occur greater than 24 hours apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures occur over the next 10 years.
- Diagnosis of an epilepsy syndrome

The basic operational seizure type classification includes Focal onset seizures (Aware/Impaired awareness; Motor/Non-motor onset; and Focal to bilateral tonic-clonic); Generalized onset (Motor/Non-motor (Absence)); and Unknown onset (Motor/Non-motor; Unclassified). (Fisher et al., 2017).

Among drug therapies for epileptic children, most epileptologists preferred traditional AEDs, such as valproate, carbamazepine, and phenobarbital in the past. However, recently, major attention has been paid to newer drugs, such as levetiracetam, topiramate, oxcarbazepine, and lamotrigine. Newer AEDs are used as monotherapy, as well as add-on therapy for children with epilepsy (DiPiro et al., 2011). Previous studies have reported the effects of traditional AEDs on thyroid hormones in children. However, there is

limited evidence regarding the effects of newer AEDs (Yilmaz et al., 2014).

Although these are well tolerated, many effects on endocrine functions have been reported in literature especially, the effect of long-term administration of anticonvulsant drugs on blood thyroid hormone levels (Alberto et al., 2009; Ramsay, 1985). Many effects on endocrine functions have been reported in literature and AEDs can result in subclinical hypothyroidism. Nowadays most commonly long-term used AEDs in children are Valproate, Oxcarbazepine, and Levetiracetam. Phenytoin, being an enzyme inducer, has been reported to reduce both free and total T3 and T4 levels (Connacher et al., 1987; Surks and DeFesi, 1996).

Though there have been studies saying that the hypothyroid state induced by phenytoin therapy is not associated with clinical features of hypothyroidism there have been recent reports of clinical hypothyroidism associated with phenytoin toxicity (Tiihonen et al., 1995; Betteridge and Fink, 2009; Collins, 2008).

Though there have been studies suggesting that carbamazepine-induced reduction in thyroid hormone levels is not associated with clinical hypothyroidism there have been studies suggesting the contrary (Verrotti et al., 2001; Isojarvi et al., 1992; Verrotti et al., 2009; Simko et al., 2007; Zhu et al., 1994).

Many effects on endocrine function have been reported in the literature. AED can result in subclinical hypothyroidism. Subclinical hypothyroidism

is defined as an asymptomatic state in which serum TSH concentration rises above the statistically defined upper limit of the reference range when free thyroxine (FT4) concentration is within its reference range (Surks et al., 2004).

Nowadays most commonly long term used AEDs in children are Valproate, Oxcarbazepine, and Levetiracetam. The present study aimed to investigate the effect of Valproate, Levetiracetam, and Oxcarbazepine monotherapy on thyroid function in children with epilepsy.

Reports on the effect of VPA on the thyroid hormone balance are conflicting, and both low and unchanged serum thyroxine (T4) and free thyroxine (fT4) levels have been found in patients receiving VPA monotherapy, never associated with overt thyroid dysfunction. Though there have been studies suggesting that carbamazepine-induced reduction in thyroid hormone levels is not associated with clinical hypothyroidism, there have been studies suggesting the contrary. The objective of the study is to assess the effect of Valproate, Levetiracetam, and Oxcarbazepine monotherapy on thyroid function in children with epilepsy.

Patients and methods

Study design: Prospective observational study. Study was performed at Tata Main Hospital, C road West Northern town, Bistupur, Jamshedpur, (Jharkhand) - 831001

Inclusion criteria:

Children in the 1-12 years age group:

1. With newly diagnosed epilepsy and being started on monotherapy with

Levetiracetam/Valproate/
Oxcarbazepine.

2. With complex febrile seizure being started on Valproate.
3. Children should be on antiepileptic for at least 1 year.

Exclusion criteria:

1. Children with a pre-existing thyroid disorder.
2. During study if 2nd AED is added.
3. Children who are non-compliant to AED or whose AED is stopped before one year
4. Children who are suffering from the liver disorder and moderate to severe PEM.
5. Children with loss of follow-up.

Study duration

This study was carried out from May 2019 to December 2020. The recruitment of all the study participants was done in the same period.

Sample size determination: n = 66

Sample size calculation for observational studies,

$$n = \frac{Z^2 (p) \times (1-p)}{d^2}$$

Where n is the sample size, Z is the statistic corresponding to the level of confidence, p is expected prevalence, and d is precision (corresponding to effect size).

Data collection techniques and tools: All the necessary information regarding the study was explained to the parents of the children. Informed written consent was taken from the parents who were willing to enrol their children in the study. Data of all children included in the study were collected in the preformed designed as per the study requirement. A baseline TFT (TSH, T3, T4) was done at the onset of

treatment. TFT was done using Radioimmunoassay (RIA) technique.

In our setup, diagnostic modalities for determining fT3 (free T3) and fT4 (free T4) were not available so we can get only T3 and T4 done.

At 6th month and 12th month post-enrollment in the study, children were assessed in detail for control of seizures and the development of any signs and symptoms of hypothyroidism. A repeat TFT was done at 6th month and 12th month follow-up.

Data Entry and analysis: All the data collected was entered into a spreadsheet on Microsoft Office Excel and later transferred to SPSS (IBM version 21.0) for analysis.

Results

Demographics of study participants: (as depicted in Fig.1,2 & Table.1)

A total of 66 study participants were included in the study. The age of the study participants varied from 1 year to 12 years with a mean (\pm SD) of 5.9 (\pm 6) years. In the study, male preponderance was seen among study subjects with 51 (77.3%) males and 15 (22.7%) females.

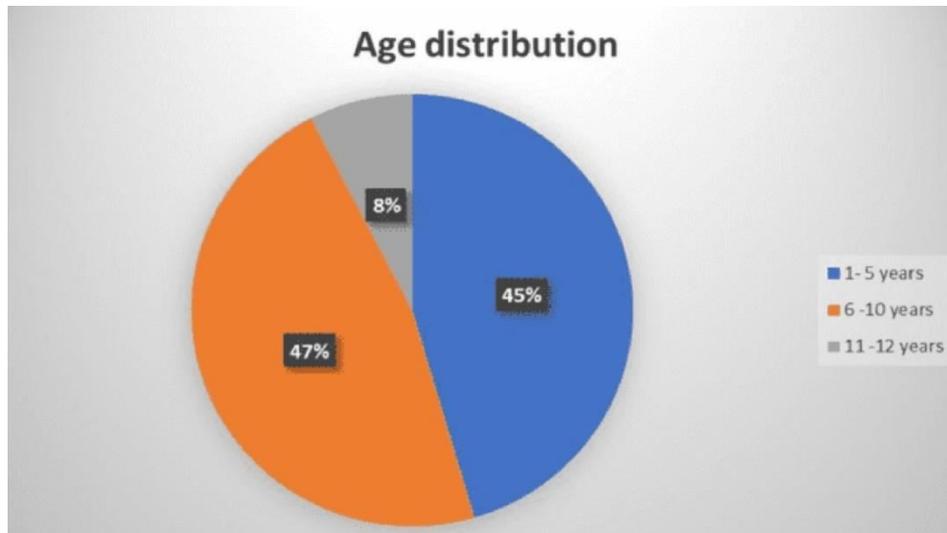


Fig.1. Age wise distribution of study participants

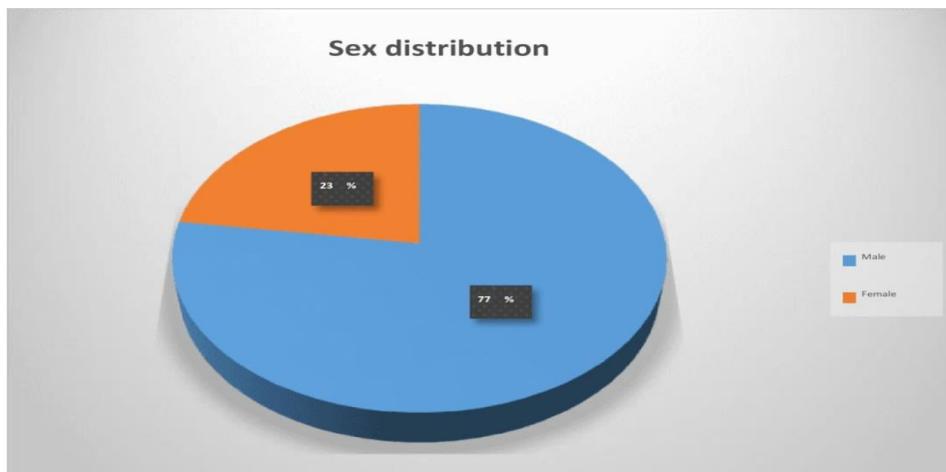


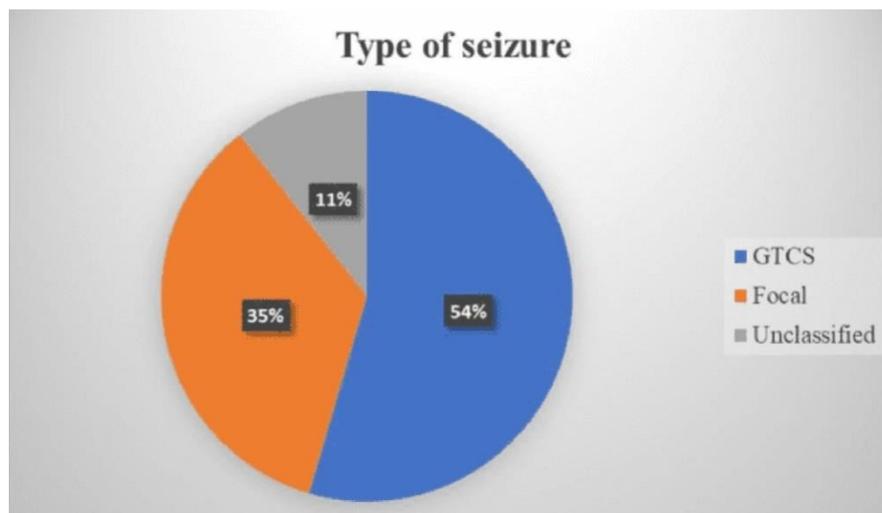
Fig. 2. Gender wise distribution of study participants

Table 1. Demographic details of study participants

Profile of study participants	N (%) (total n=66)
Age group (in years)	
• 1-5 years	30(45)
• 6-10 years	31(47)
• 11-12 years	5(8)
Gender	
• Male	51(77.3)
• Female	15(22.7)
Residence	
• Urban	37(56.1)
• Rural	29(43.9)

Among the study participants, generalized onset tonic-clonic seizures (GTCS) were

seen in 36 (54%) subjects and Focal onset seizures in 23(35%) cases. **(Fig.3)**

**Fig.3. Distribution of type of seizures among study participants**

As an antiepileptic therapy, Valproate was administered to 34 (51.5%), levetiracetam to 24 (36.4%), and oxcarbazepine to 8(12.1%) study subjects. **(Fig.4)**.

Statistical Analysis was done to find any significant difference in thyroid function tests between baseline levels and

after 6 months of antiepileptic treatment. A significant increase in TSH levels was found post-treatment as compared to baseline levels, indicative of a suppressive effect on thyroid activity. This was found to be statistically significant. **(Table.2,3,4)**

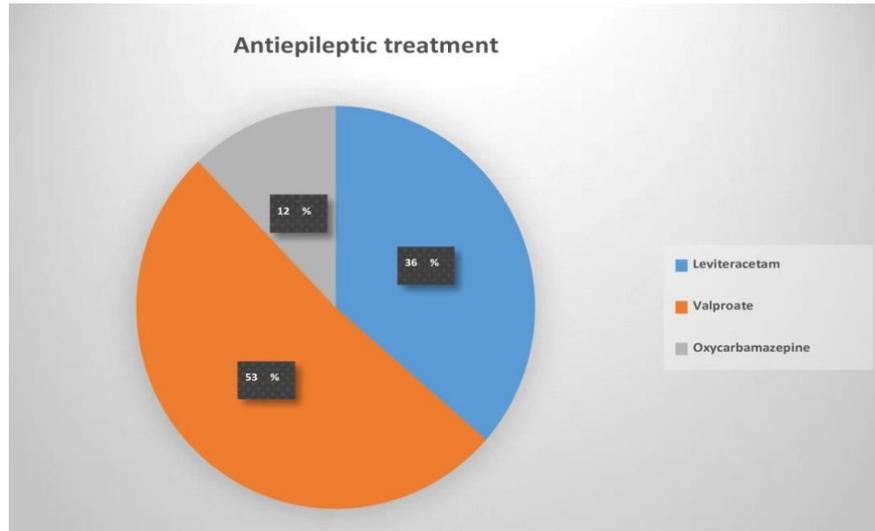


Fig.4. Treatment wise distribution of the study participants

Table 2. Baseline thyroid function tests of study participants (n=66)

Baseline thyroid function test	Mean (\pm SD)	Minimum	Maximum
TSH	1.7(\pm 0.45)	0.8	3.2
Total T3	3.04(\pm 0.58)	1.6	4.2
Total T4	8.05(\pm 2.3)	3.6	13

Table 3. Thyroid function tests of study participants at 6th month

Thyroid function test-6 months	Mean (\pm SD)	Minimum	Maximum
TSH	3.17(\pm 0.654)	2.1	4.4
Total T3	3.4(\pm 0.30)	3.1	4.2
Total T4	1.4(\pm 0.77)	1.2	1.7

Table 4. Effect of 6 months of antiepileptic therapy on Thyroid function tests

TFT	Mean (+ SD)	T value	p-value
TSH Baseline At 6 months	1.7(\pm 0.45) 3.17(\pm 0.65)	-12.17	0.000
T3 Baseline At 6 months	3.04(\pm 0.58) 3.41(\pm 0.3)	0.702	0.485
T4 Baseline At 6 months	8.05(\pm 2.37) 1.44(\pm 0.15)	-0.596	0.553

Paired t- test applied, p value < 0.05 is significant

Statistical Analysis was done to find any significant difference in thyroid function tests between baseline levels and after 12 months of antiepileptic treatment. A significant increase in TSH & reduction

in T4 levels were found post-treatment as compared to baseline levels, indicative of a suppressive effect on thyroid activity. This was found to be statistically significant.(Table.5,6)

Table 5. Thyroid function tests of study participants at 12th month

Thyroid function test-12 months	Mean (\pm SD)	Minimum	Maximum
TSH	4.9 (\pm 0.77)	3.5	6.6
Total T3	3.2 (\pm 0.43)	2.1	3.7
Total T4	5.9 (\pm 3.09)	2.3	13

Table 6. Effect of 12 months of antiepileptic therapy on Thyroid function tests

TFT	Mean (\pm SD)	<i>T value</i>	<i>p-value</i>
TSH Baseline At 12 months	1.7 (\pm 0.45) 4.9 (\pm 0.65)	-30.17	0.000
T3 Baseline At 12 months	3.04(\pm 0.58) 3.2 (\pm 0.43)	1.793	0.485
T4 Baseline At 12 months	8.05 (\pm 2.37) 5.9 (\pm 3.09)	4.515	0.000

Paired t-test applied, p value < 0.05 is significant

(Table.7) depicts the comparison of the effect of various antiepileptic drugs on the three parameters of the thyroid function test at the 12th month of the therapy. ANOVA test was applied to find the difference in thyroid function test values at 12 months, among the

three anti-epileptic drugs: Valproate, Levetiracetam, and oxcarbazepine. It was found from the analysis that there was no significant difference in the effect of the 12 months of therapy by any of the three anti-epileptic drugs, on TSH, total T3, and total T4 values.

Table 7. Comparison of the effect of various antiepileptic drugs on thyroid function tests at 12th month of the therapy

Variables	Mean(SD)	F value	p value
TSH			
• Valproate	3.2(±0.63)	0.558	0.575
• Levetiracetam	3.1(±0.61)		
• Oxcarbazepine	3.0(±0.93)		
T3			
• Valproate	3.4(±0.28)	1.267	0.289
• Levetiracetam	3.4(±0.32)		
• Oxcarbazepine	3.2(±0.18)		
T4			
• Valproate	1.4(±0.16)	0.966	0.386
• Levetiracetam	1.4(±0.15)		
• Oxcarbazepine	1.4(±0.14)		

ANOVA test applied, p value<0.05 is significant

Discussion

The study was done to assess the effect of valproate, levetiracetam, and oxcarbazepine monotherapy on thyroid function in children with epilepsy. Our study has depicted a significant suppressive effect on thyroid function in the study subjects after antiepileptic therapy as depicted by an increase in TSH after 6 months of therapy and an increase in TSH with a decrease in T4 after 12 months. Several similar studies in the recent past have reported similar findings.

A study by **Das et al (2018)** reported that the Mean ± SD of TSH levels significantly increased after six months of antiepileptic therapy in comparison to the baseline values [1.76±0.57 µiu/ml. versus 2.70±1.50µiu/ml.] and with control group at follow up visit [1.74±0.73µiu/ml vs2.70±1.50µiu/ml].

A study done by **Ranga et al (2015)** reported that a significant

difference was observed in mean ft4 values between the epileptic and the control groups. On the other hand, a study by **Bentsen et al (1983)** reported that during treatment with carbamazepine, a significant decrease in T4, ft4, ft3, rt3, and TBG was observed.

A study done by **Dhodi et al (2016)** reported that patients on Phenytoin showed TSH values (Mean ± SD) to be statistically higher than the baseline and the normal reference value, whereas no significant difference was noted in the serum ft3 and ft4 values.

A similar study by **Yilmaz et al (2014)**, showed a reduction in the serum ft4 and an increase in the serum TSH levels with valproate, carbamazepine, and phenobarbital administration, but not levetiracetam.

A similar study by **Adhimoolam and Arulmozhi (2012)** evaluating adult epileptic patients reported similar findings in which the study subjects were

administered traditional AEDs, including valproate, carbamazepine, and phenytoin.

We found that none of our patients developed overt symptoms of hypothyroidism, and all patients were clinically euthyroid. According to previous studies, subclinical hypothyroidism may develop in epileptic patients during treatment with AEDs. However, no symptoms or signs of hypothyroidism were reported. (El-Farahaty RM et al., 2015; Kim SH et al., 2012)

Conclusion

This study has depicted a negative effect of antiepileptic therapy on the Thyroid function in children as evidenced by a significant post-treatment reduction in TSH and T4 levels. Because of the findings of this study we recommend a Baseline evaluation of Thyroid function of all children with epilepsy who are subjected to Anti Epileptic Drug therapy. Through clinical examination at each visit to look for any signs and/or symptoms of hypothyroidism and through biochemical tests (Sr TSH, Total T3, Total T4) if needed. Sr TSH is to be done annually to detect subclinical hypothyroidism.

Conflict of interest: None declared

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References

- **Adhimoolam M, Arulmozhi R. (2016).** Effect of antiepileptic drug therapy on thyroid hormones among adult epileptic patients: An analytical cross-sectional study . J Res Pharm Pract, 5: 171-4.
- **Alberto V, Melissa L, Alessandra S, Emilio F, Francesco C. (2009).** Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate . Euro J Endocrinol, 160:81-86.
- **Bentsen KD, Gram L, Veje A. (1983).** Serum thyroid hormones and blood folic acid during monotherapy with carbamazepine or valproate. A controlled study. Acta Neurol Scand, 67(4):235-41.
- **Betteridge T, Fink J. (2009).** Phenytoin toxicity and thyroid dysfunction . NZ Med J, 122(1303):102-4.
- **Collins RJ. (2008).** The elevated thyroid-stimulating hormone in a 65-year-old patient with phenytoin toxicity . Consult Pharm, 23(8):610-3.
- **Connacher AA, Dorsey DQ, Browning MCK, Davidson DLW, Jung RT. (1987).** The effective evaluation of thyroid status in patients on phenytoin, carbamazepine, or sodium valproate attending an epilepsy clinic . Postgraduate Medical Journal, 63:841-46.
- **Das D, Ahmed MM, Chowdhury PK, Dutta PK, Chowdhury MA. (2018).** Subclinical Hypothyroidism During Valproic Acid Therapy in Children with Epilepsy . ChattagramMaa-O-Shishu Hospital Med Col Journal, 17(2):1-3
- **Dhodi DK, Bhagat SB, Patil KC. (2016).** A comparative study of thyroid status of patients on phenytoin, and carbamazepine (2016). Pharmacol, 5: 362- 65.
- **DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM**

- (2011). Pharmacotherapy, A pathophysiologic approach. 8th ed., USA: McGraw Hill; 2011.
- **El-Farahaty RM, El-Mitwalli A, Azzam H, Wasel Y, Elrakhawy MM, Hasaneen BM. (2015).** Atherosclerotic effects of long-term old and new antiepileptic drugs monotherapy: a cross-sectional comparative study . J Child Neurol, 30: 451-7.
 - **Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. (2017).** Operational classification of seizure types by the international league against epilepsy: Position paper of the ILAE Commission for classification and terminology. Epilepsia.58:522-30.
 - **Isojarvi JIT, Pakarinen AJ, Myllyla VV. (1992).** Thyroid function with antiepileptic drugs (1992). Epilepsia, 33:142-8.
 - **Kim SH, Chung HR, Kim SH, Kim H, Lim BC, Chae JH, et al. (2012).** Subclinical hypothyroidism during valproic acid therapy in children and adolescents with epilepsy (2012). Neuropediatrics,43:135-9.
 - **Yılmaz TS, Akıncı G, Korkmaz HA, Tekgül H. (2014).**The effect of antiepileptic drugs on thyroid function in children. Seizure. 2014;23(1):29–35
 - **Ramsay I. (1985).** Drug and non-thyroid-induced changes in thyroid function tests(1985). Postgrad Med J, 61: 375- 77.
 - **Ranga S, Ahluwalia C, Harini D, Choudhry IP, Aggarwal KC.(2015).** Hypothyroidism in children with epilepsy on valproate monotherapy in the age group of 3-12 years. MedPulse-International Medical Journal, 2(12): 840-843.
 - **Simko J, Horacek J. (2007).** Carbamazepine and risk of hypothyroidism: a prospective study (2007). Acta Neurol Scand, 116 (5): 317-21.
 - **Surks MI, DeFesi CR. (1996).** Normal serum free thyroid hormone concentrations in patients treated with phenytoin or carbamazepine: A paradox resolved (1996). JAMA, 275(19):149-58.
 - **Surks MI, Ortiz E, Daniels GH, et al. (2004).** Subclinical thyroid disease: scientific review and guidelines for diagnosis and management . JAMA, 291 (2):228-38.
 - **Tiihonen M, Liewendahl K, Waltimo O, Ojala M, Välimäki M. (1995).** Thyroid status of patients receiving long-term anticonvulsant therapy assessed by peripheral parameters: a placebo-controlled thyroxine therapy trial . Epilepsia, 36(11):1118-25.
 - **Verrotti A, Basciani F, Morrresi S, Morgese G, Chiarelli F. (2001).**Thyroid hormones in epileptic children receiving carbamazepine and valproic acid . Pediatric Neurology, 25:43-6.
 - **Verrotti A, Laus M, Scardapane A, Franzoni E, Chiarelli F. (2009).** Thyroid hormones in children with epilepsy during long-term administration of

carbamazepine and valproate . Eur
J Endocrinol, 160(1):81-6.

- **Zhu S, Liu X, Ruan X, Cai Z. (1994).** Changes of thyroid hormone

levels in epileptic patients . Journal
of Tongji Medical University,
14:119-23.