Original article:

A Prospective, Randomized, open label, comparative study of Amitriptyline, Pregabalin and sodium Valproate in Patients with painful Diabetic neuropathy

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ABSTRACT:

Background: Diabetes is a leading cause of neuropathy which causes pain and impairs an individual's sleep, mood, and has a negative impact on daily activities, resulting in poor quality of life.

Objectives: To compare the efficacy,safetyand effect on sleep&mood of Amitriptyline, Pregabalin and sodium Valproate in Patients with painful Diabetic neuropathy

Methodology: A prospective, randomized, open label, comparative study of 6 weeks duration included newly diagnosed cases of painful Diabetic Neuropathy. Baseline history, clinical examination, pain evaluation and laboratory tests was done . Dose escalation of drugs , Subjective pain assessment by 0-l0 numeric pain rating scale and Subjective sleep, mood, daytime sleepiness by Leeds Sleep Evaluation Questionnaire were done at every 2 weeks intervals.

Conclusion: Amitriptyline, Pregabalin didn't differ significantly in terms of pain relief but pregabalin has less side effects than amitriptyline. Sodium evaporate is less efficacious in relieving diabetic neuropathy pain but it doesn't produce much day time sleepiness. So it can be considered as choice in patients with seizures ,migraine , manic depressive illness who develop neuropathy.

Keywords: Diabetic Neuropathy**,** Leeds Sleep Evaluation Questionnaire

INTRODUCTION:

Diabetes is a leading cause of neuropathy. Around 50% of diabetic patients develop peripheral neuropathy in 25 years(l).Chronic diabetic peripheral neuropathic pain (DPNP) is a common, debilitating, and distressing complication of diabetes. In addition to directly causing pain, it can also impair an individual's sleep, lower mood, and have a negative impact on daily activities,resulting in poor quality of life.Treatment regimens of chronic diabetic peripheral neuropathic pain (DPNP) is often inadequate at controlling pain and limited by side effects and drug tolerance.(2)

Apart from glycemic control, current guidelines recommend the use of antidepressants and anticonvulsants in the treatment of Diabetic peripheral neuropathic Pain(3).Although amitriptyline a tricyclic antidepressant ,has been shown to be efficacious in the treatment of neuropathic pain , its relative nonspecific mode of action may limit its use due to a broad range of adverse effects.(4).Pregabalin is predominantly excreted into the urine without hepatic metabolism. So dose adjustment is needed in patients with impaired renal function.(5)(6).Sodium Valproate can be given without much dose adjustment in the presence of chronic kidney disease..(Diabetic nephropathy and nephropathy are common in chronic diabetic population). According to

American Academy of NeurologySodium Valproate is given as (level B) recommendations for the management of diabetic peripheral neuropathy. .(7).Sodium valproate will also be beneficial in the presence of co morbid illness like migraine/ chronic headache and seizure disorder.

There are studies which compared pregabalin ,gabapentin, duloxetine (8), but there are not much studies which compares amitriptyline ,pregabalin, sodium valproate

Therefore, it was decided to compare the efficacy and safety of Amitriptyline, and Pregabalin and Sodium Valproate in patientswith painful Diabetic neuropathy to provide an appropriate treatment option in such patients.

Objectives:

- To compare the efficacy of Amitriptyline, and Pregabalin and sodium Valproate in Patients with painful Diabetic neuropathy
- To compare the safety of these drugs in Patients with painful Diabetic neuropathy .
- To compare the effect of the drugs on sleep, mood, and daytime sleepiness and improvement in overall status .

METHODOLOGY :

Study design: Prospective, Randomized,open label , comparative study

Study centre: Chengalpattu medical college & Hospital

Study population: Patients with diabetic neuropathy attending neurology Out Patient Department.

Sample size: 150 patients

Study duration: 6 weeks

Study period: June 2017- December 2017

Inclusion criteria:

- Newly diagnosed cases of painful Diabetic neuropathy with type 1 or type 2 diabetes
- Age 18-60 yrs
- Both sex
- Patients willing to give informed consent

Exclusion criteria:

- Alcoholic
- Substance abuse
- Hb A1C > 7.5
- Chronic liver/kidney disease or any other major health problems.
- On psychiatric medication
- Other causes of neuropathy like drug induced , B12 deficiency
- Pregnancy, lactation
- Age >60yrs
- Patients not willing to give informed consent
- Women those have not yet completed their family

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- Diabetes with acute complications

After getting approval from institutional ethics committee, this trial was conducted according to Good Clinical Practice Guidelines. Subjects who give informed consent was recruited on the basis of detailed history , clinical and neurological examination .A confirmation of diabetic Peripheral Neuropathy was made by means of DN4 questionnaire(10) score >4 . Among them , Patients who fulfilled the inclusion / exclusion criteria was randomized by computer generated randomization table into the three treatment groups, with the dose range of amitriptyline, - 25 -75 mg/day, pregabalin -75 – 300 mg/day, sodium valproate- 400 - 1200 mg/day (9).Basline history,clinical examination ,pain evaluation,sleep pattern and laboratory tests weredone .Dose escalation done at 2 weeks intervals till patients relieved of symptoms or develop unacceptable side effects.Pain evaluationand effect of drugs on sleep & day time activity wasassessed at every 2 weeks intervals by appropriate scale and questionnaire. Compliance was checked by pill counting . Patients were advised to report the side effects to the investigator.Laboratory parameters wasrepeated at the end of the study.

Assessment of Outcome:

Assessment of efficacy : Severity of pain is assessed by 0-l0 numeric pain rating scale (10).Subjective sleep, mood, and daytime sleepiness was assessed by Leeds Sleep Evaluation Questionnaire (l1) which contains 4 parametres Getting to sleep (GTS),Quality of sleep (QOS), Awake following sleep (AFS), Behaviour following wakening(BFW)

Assessment of Safety: Adverse drug reactions (ADRs) reported by the patients are noted. Causality analysis of Adverse drug reactionswas done by Naranjo's algorithm andby assessing laboratory parameters at the end of the study.

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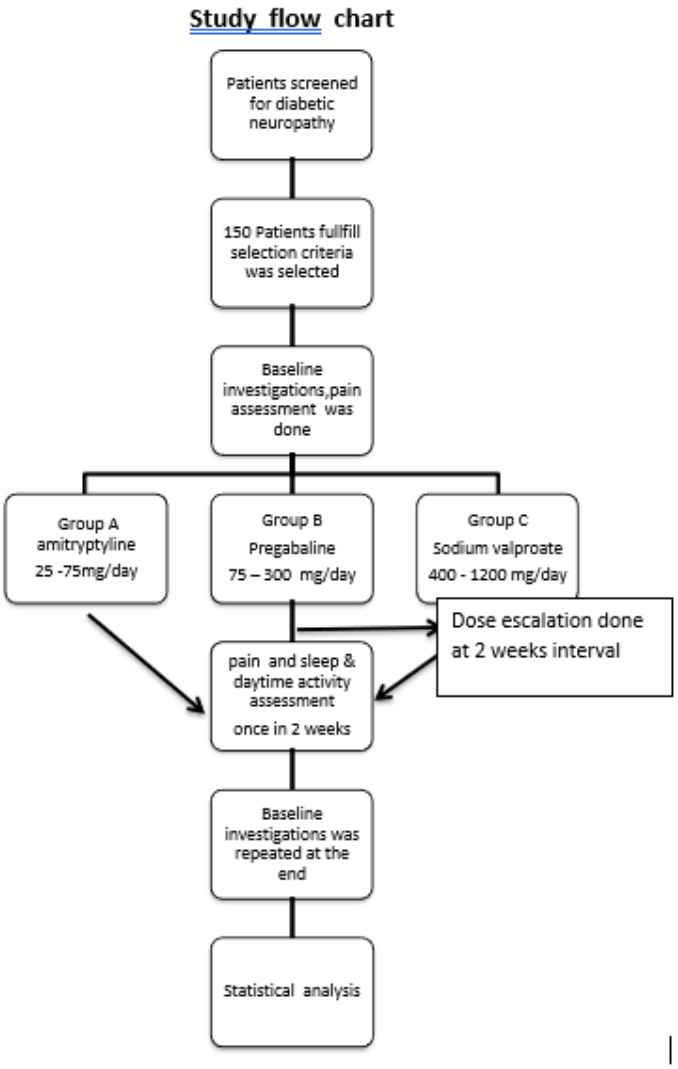

RESULTS:

Intention to treat analysis was done . There were 3 dropouts in amitriptyline group, 1 in pregabalin group, 2 in sodium valproate group due to side effects.

TABLE 1: DEMOGRAPHIC PARAMETERS OF SUBJECTS

ONE WAY ANOVA		Sum of Squares	df	Mean Square	F	Sig.
Age	Between Groups	52.253	2	26.127	1.464	.235
	Within Groups	2623.640	147	17.848		
	Total	2675.893	149			
BMI	Between Groups	4.028	2	2.014	1.310	.273
	Within Groups	222.965	145	1.538		
	Total	226.993	147			
HBA1C	Between Groups	.122	2	.061	.332	.718
	Within Groups	27.044	147	.184		
	Total	27.166	149			

TABLE 2:REPEATED MEASURES ANOVA WITH POST HOC ANALYSIS - PAIN

Measure: pain						
Tukey HSD						
(I) treatment	(J) treatment	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
ami	pre	.01	.148	.999	-.34	.36
	val	-.45*	.148	.007	-.80	-.10
pre	ami	-.01	.148	.999	-.36	.34
	val	-.46*	.148	.007	-.81	-.11
val	ami	.45*	.148	.007	.10	.80
	pre	.46*	.148	.007	.11	.81

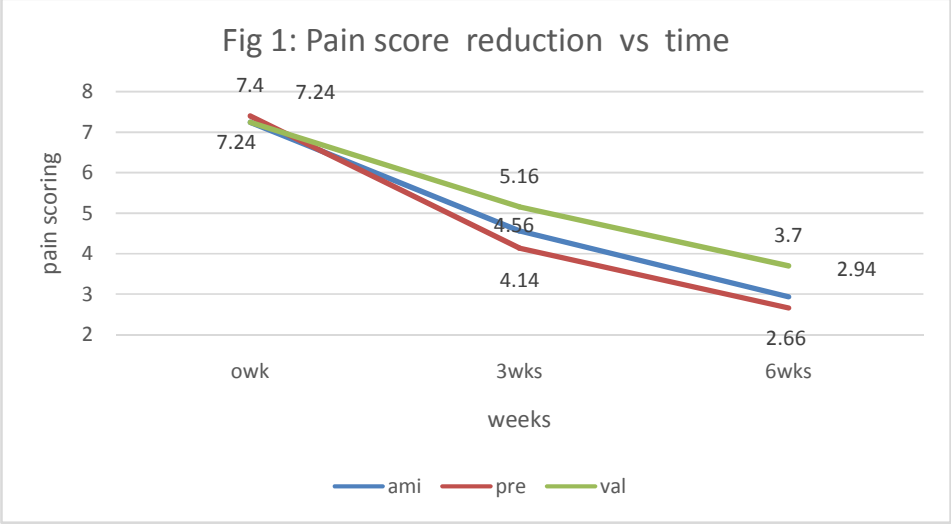

TABLE3:REPEATED MEASURES ANOVA WITH POST HOC ANALYSIS – GTS ,QOS,AFS,BFW

Tukey HSD						
Measure	(I) treatment	(J) treatment	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval
						Lower Bound
GTS	ami	pre	.327	.4261	.724	-.682
		val	4.400*	.4261	.000	3.391
	pre	ami	-.327	.4261	.724	-1.336

		val	4.073*	.4261	.000	3.064
	val	ami	-4.400*	.4261	.000	-5.409
		pre	-4.073*	.4261	.000	-5.082
QOS	ami	pre	.353	.2483	.332	-.235
		val	3.933*	.2483	.000	3.345
	pre	ami	-.353	.2483	.332	-.941
		val	3.580*	.2483	.000	2.992
	val	ami	-3.933*	.2483	.000	-4.521
		pre	-3.580*	.2483	.000	-4.168
AFS	ami	pre	-1.507*	.1964	.000	-1.972
		val	-1.713*	.1964	.000	-2.178
	pre	ami	1.507*	.1964	.000	1.042
		val	-.207	.1964	.545	-.672
	val	ami	1.713*	.1964	.000	1.248
		pre	.207	.1964	.545	-.258
BFW	ami	pre	-1.580*	.3529	.000	-2.416
		val	-1.667*	.3529	.000	-2.502
	pre	ami	1.580*	.3529	.000	.744
		val	-.087	.3529	.967	-.922
	val	ami	1.667*	.3529	.000	.831
		pre	.087	.3529	.967	-.749

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FIG: 2 GTS ,QOS,AFS,BFW SCORE VS TIME

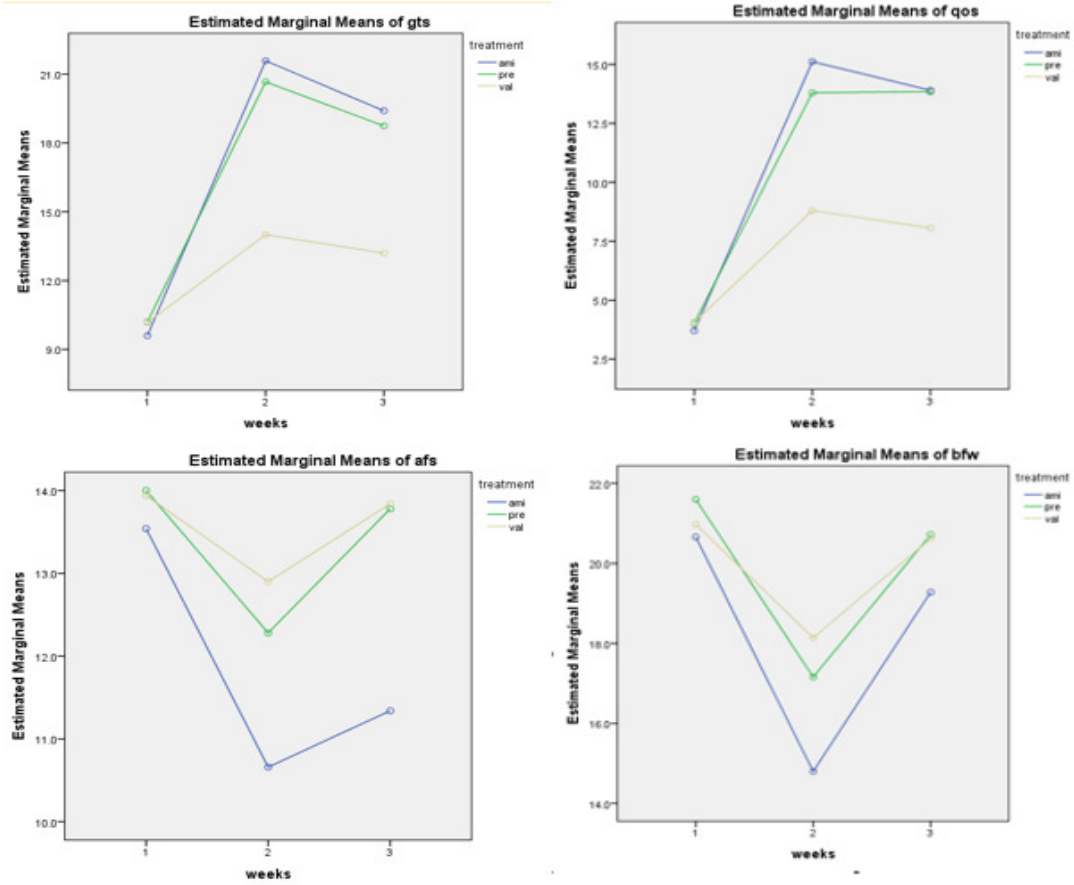

TABLE 4: ADVERSE EFFECTS

Amitriptyline	Pregabalin	Sodium valproate
Drowsiness – 58%	**Drowsiness – 32%**	**Fatigue – 28%**
Sedation-44%	**Pedal edema – 8%**	**Hair loss – 22%**
Giddiness – 36%		**Weight gain – 18%**
Dry mouth – 32%		**Irregular menstrual cycle- 14%**
Loss of taste – 24%		**Tremor-4%**
Difficulty in urination – 12%		**Thrombocytopenia- 2%**
Constipation – 6%		

DISCUSSION:

Hyperglycemia is highly correlated with the development and progression of all neuropathies, including Peripheral Diabetic Neuropathy. The Diabetes Control and Complications Trial (DCCT) showed that tight glycemic control will reduce the incidence of neuropathy by 60%.However, even in patients with long-term excellent glycemic control (A1C < 8%), the lifetime incidence of Peripheral Diabetic Neuropathy remains 20%.

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In this study we compared efficacy , safety and effect of drugs on sleep of 3 drugs amitriptyline, - 25 -75 mg/day, pregabalin -75 – 300 mg/day,valproate- 400 - 1200 mg/day for 6 weeks

In our study, amitriptyline and pregabalin have shown good pain relief in diabetic neuropathic patients compared to sodium valproate. Comparing Amitriptyline and Pregabalin, there is no statistical significance in pain relief whereas sodium valproate response to diabetic pain is inferior to other two drugs. Pregabalin group showed better pain relief compared to amitriptyline but there is no statistically significant difference seen .We used leeds sleep evaluation questionnaire (LSEQ), to assess the side effect profile of these three drugs. Getting To Sleep (GTS) in LSEQ, amitriptyline and pregabalin scored high than sodium valproate in statistically significant manner throughout our study period of 6 weeks. This is due to better pain relief and more sedative side effects of amitriptyline and pregabalin compared to sodium valproate. (Usually diabetic neuropathic pain is more severe during night time than day time).Quality Of Sleep (QOS) in LSEQ , amitriptyline and pregabalin scored higher than sodium valproate (statistically significant) during six week study period.Again we can attribute this one to better pain relief and more sedative side effects of amitriptyline and pregabalin. Awakening Following Sleep (AFS) in LSEQ , amitriptyline scored less than pregabalin and sodium valproate (statistically significant) ; it means more difficult than usual awakening and requires a period longer than usual awakening. We can attribute this one to more drowsiness of amitriptyline compared to other two drugs.

Behaviour Following wakening (BFW) in LSEQ, amitriptyline scored less than pregabalin and sodium valproate (statistically significant) and it means more tired and more disrupted in balance and coordination upon awakening throughout our 6 weeks study period. The overall efficacy was comparable for both pregabalin and amitriptyline, except for the intensity of adverse events. Dose escalation with amitriptyline was limited by its adverse effects (especially dry mouth).). Lab parameters didn't differ significantly before and after the study.

CONCLUSION:

According to our study even though pregabalin and amitriptyline are equally efficacious , pregabalin is superior to amitriptyline in terms of adverse effects.

Sodium valproate is less efficacious in relieving pain than other 2 drugs , but can be used when other coexisting illnesses are present.. However further studies with long duration with large population are needed to confirm this

Sponsorship: No

Conflict of interest: No

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