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Comparison of Pregabalin- Methylcobalamin with Gabapentin-Methylcobalamin Therapy in Diabetic Neuropathy: A Prospective Study on Quality of Life

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ABSTRACT

Diabetic neuropathy has been reported as the most common complication of Diabetes mellitus. The antiepileptic agents along with the neurotrophic agents have been widely used for diabetic neuropathy. The aim of the study was to evaluate the efficacy of the mostly prescribing Pregabalin and Gabapentin with methylcobalamin. It was a prospective study including 200 patients considering 100 in each group. The primary outcome measure was the neuropathic pain scale. Secondary measure included the RAND36 measuring quality of life. Among the total cases collected, females were the highly affected population and patients under the age group of 60-69 years were highly prevalent. The majority of the patients had numbness and aching type of pain distributed in the lower extremities involving foot, toes,hip, leg etc. Hyperglycemia was considered as the major cause of DN. For the primary outcome variable, change in the NPS score was considered. The mean pain score at baseline was almost similar between treatment groups. Among both groups pain score was reduced at the end of the study indicating the pain relieving effect of both therapy. The change in QoL from baseline to the final week was measured in the RAND36 questionnaire. Significant improvement in QoL was reported in both treatment groups. The difference in this improvement among both groups shows a discrepancy. It may be due to the adverse reactions of the therapy. These discrepancies leave us with an equivocal result with regard to the efficacy of treatment groups in improving the QoL.

Keywords: Diabetic mellitus, Diabetic neuropathy, pregabalin, gabapentin, methylcobalamin, hyperglycemia, Neuropathic pain scale, Quality of life

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INTRODUCTION

Diabetes is a globally prevalent condition and its prevalence in adults worldwide was estimated to be 4% in 1995 and expected to rise to 5.4% by the year 2025. Neuropathy is considered as the most common micro-vascular complications of both types diabetes mellitus (DM). In 40-50 % of people with diabetes mellitus type1 or type 2, neuropathy develops within 10 years of onset.

Two main types of Diabetic Neuropathy(DN) involves, the autonomic and somatic nervous system. The most common type of DN is somatic or sensorimotor neuropathy with peripheral symptoms of burning sensation, shooting, tingling and allodynia. Neuropathic pain (NeP) shows a negative impact on the Quality of Life (QoL). The primary cause of DN is thought to be hyperglycemia. So improved glycaemic control is the main stay of efforts to be effective in slowing the progression of DN. Attempts to treat DN can be divided into those Divided into those directed towards the modification of the underlying disease process and those directed towards symptom suppression.

The evidence-based guideline addresses the efficacy of pharmacological and non-pharmacological treatments for reducing pain and improving physical function and Q0L in patients with PDN. Some patients with NeP respond well to treatment and others show no obvious response. The pharmacologic agents include anticonvulsants, antidepressants, opioids, anti-arrhythmics, cannabinoids, aldose reductase inhibitors, protein kinase C beta inhibitors, antioxidants (α-lipoic acid), transketolase activators, topical medications and others. The nonpharmacologic modalities include infrared therapy, shoe magnets, exercise, acupuncture, external stimulation, spinal cord stimulation, biofeedback and behavioral therapy, surgical decompression, and intrathecal baclofen. More recently, the use of anticonvulsants has been proposed as the firstline for the treatment of NeP.

Their effectiveness in NeP syndrome is not surprising as both epilepsy and NeP can arise because of abnormal neuronal activation following an insult to nerve cell. Pregabalin (PG) and gabapentin (GP) have been shown to be effective in the treatment of NeP. The addition of neurotrophic agent containing methylcobalamin (MC), L-methylfolate, pyridoxal 5-phosphate would increases pain relief when given to subjects using the anticonvulsants like GP & PG for the treatment of painful DN. Considering all these factors a study was attempted for comparing the efficacy of the mostly prescribing combination of the anticonvulsants, PG and GP along with the neurotrophic agent MC when used in patients with DN.

MATERIALS AND METHOD

Study site:

The study was carried out in the Palakkad Diabetic Centre, Palakkad.

Study population:

Diabetic neuropathy patients attending Palakkad Diabetic Centre receiving PG+MC and GP+MC therapy above 18 years of age were included in the study.

Study design:

It was a prospective observational study. The data collection was for a period of six months (January2014- July 2014) with the help of a pre-designed patient data entry form and by direct personal interview. Neuropathic pain scale (NPS) & RAND36 were used as the primary & secondary outcome measure. Informed consent was taken when the interview was conducted. The study was approved by institutional ethics committee – GCP/IEC/625/2014.

Statistical Analysis:

Descriptive statistics, such as percentage, mean and standard deviations were used for describing the study variables. Chi-square and t-test were performed to find out the significance of the data by using "Graph Pad Instat" version 3.10 and SPSS20.

RESULTS AND DISCUSSION

A total of 220 patients were included in the study, 20 cases excluded due to the reason that of cannot get proper follow up. In the 200 patients 100 were receiving Pregabalin+ methylcobalamin and another 100 were receiving Gabapentin + methylcobalamin therapy. Table 1&2 lists the demographic and baseline characteristics of the study population. Patients in both groups were well balanced by demographic factors. Both the study group comprised of 34% males & 66% females with the median age if 60 years. It was in agreement with the results published by D Rao et al., Francisco J et al.38% of the patients among both groups were under the age group of 60-69. Antonio Gatti et al & A Razi et al. study showed that the advanced age group people are more vulnerable to neuropathy. In the group receiving PG+MC therapy, 50 % patients were reported with Hypertension and 41% with Dyslipidemia. In the GP+MC therapy 40% of patients were having Hypertension and 34 % with Dyslipidemia. 29 % of the patients among both groups were without any co-morbidity. This study results are co-related with the results obtained by the study conducted by Elbert S Huang et al & Mitchell B Max et al. In PG+MC therapy 13% and 11% of the patients were smokers & alcoholics respectively. 8% smokers and 12% alcoholics were reported in the group receiving GP+MC therapy. The similar

results were observed in a study conducted by Arindam Dutta et al. All the patients in this study had neuropathic symptoms of more than or equal to 1. Among both groups 64 % of the patients having numbness as the major symptom followed by aching pain ie, 42% in PG+MC and 63% in GP+MC therapy. Pinpricking sensation was the further common symptom shown by majority of people followed by burning sensation, cramping and itching. Similar results were shown in the studies conducted by Candis M Morello et al. Mitchell B Max et al. Neuropathic symptoms were mostly reported in the lower extremities like pelvis, hip, thigh, knee, ankle and foot. Upper extremities were affected not as much of lower extremities among both groups. Similar results were observed in a study conducted by Joseph C Arezzo et al. The mean duration of DM was 12.86 & DN was 3.09 years in the patients receiving PG+MC therapy. GP+MC therapy patients were reported with a mean duration of 11.61 for DM and 2.54 years for DN. Joseph C Arezzo et al. & Joel Raskin et al. study shows the similar results of duration of DM & DN.The blood glucose level of the treatment group PG+MC shows a mean value of 145.03 for FBS & 209.26 for PPBS. The GP+MC therapy shows 145.27 for FBS & 199.83 for PPBS. Both the values are on the higher side showing hyperglycemia. The similar results were observed in a study conducted by Arindam Dutta et al. The primary outcome measure used in this study was NPS having 10 categories of pain ie, pain intensity, sharp pain, hot pain, dull pain, cold pain, sensitive pain, itchy pain, pain unpleasantness, deep pain and surface pain. The pain score of each category are taken and mean values were calculated for the baseline and endpoint. Table 3 represents baseline and endpoint mean of the NPS items with their mean difference. Significant ($P<0.05$) improvement was reported from baseline to the endpoint of the study among both groups. Figure 1 shows the mean change of NPS score. Mean change of 2.53 was reported for surface pain as the highest difference in PG+MC therapy & a mean change of 1.77 was reported for pain intensity as the highest difference in GP+MC therapy. A very smallest difference of 0.02 & -0.02 were reported for sensitive pain among patients receiving PG+MC & GP+MC therapy. Significant mean change of P value < 0.05 was observed for hot pain, cold pain, pain unpleasantness & surface pain between both groups. The results shows similarities with the study conducted by Miroslav Backonja et al. Mark Davies et al. & Michael Rowbotham ET al. Table 4 shows the mean value of the NPS score at each follow up. Among both groups, baseline mean value was higher than the mean value of all the follow-ups. Significant differences in the value were seen in the second and third follow up. A mean value of 2.51 with a SD of 1.62 & 2.83 with a SD of 1.96 were reported as the baseline score in patients receiving PG+MC & GP+MC therapy. Figure 2 shows a decrease in the mean value to each follow up. The results shows

similarities with the study conducted by Padmini Devi et al. Table 5 shows the difference in the NPS mean value of baseline with each follow up. A total of three differences were calculated for both groups. It shows a significant difference among the groups. Figure 3 shows an increase in the difference with each follow up. Highest value of 1.28 & 0.87 were reported for PG+MC & GP+MC therapy respectively. The results shows that the pain reduction is more seen in PG+MC therapy. The results shows similarities with the studies conducted by Michael Rowbotham te al. Mitchell B Max et al. & Joel Raskin et al. Table 6 shows the characteristics of the secondary outcome measure used in this study i. e. RAND36. The baseline and endpoint mean value of the 8health domains were reported with their mean difference. A significant improvement in PF, BP, VT, RE & MH were reported in patients receiving PG+MC therapy. Significant improvement of PF, BP, GH, VT & MH were reported in the group receiving GP+MC therapy. Improvements in QoL were seen among the groups after receiving the therapy. Highest mean difference of 15.76 with SD of 31.19 & 13.62 with SD of 26.78 were reported for BP in patients receiving PG+MC & GP+MC therapy respectively. A least difference of -5.08 & -3.2 were reported for RE in patients receiving PG+MC & GP+MC therapy respectively. Non significant P values were reported for the mean change among both groups. Although non significant the value shows an improvement in QoL for both groups. Figure 4 shows the difference in mean change of both population from the baseline to the final week of the study. The similar type of results were discussed in a study conducted by Miroslav Backonja et al. Table 7 shows the adverse drug reactions associated with both therapies. Dizziness and somnolence was reported as the major ADR among both groups. Dizziness was reported with 6% of the patients receiving PG+MC therapy and 4% of patients receiving GP+MC therapy. The similar results were shown in the study conducted by Miroslav Backonja et al. & Antonio Gatti et al.

Table 1: Socio demographic characteristics of study population

Sl No	Parameter	No of cases(n)		P value
		PG+MC	GP+MC	
1	**Gender**			1.000
	Male	34	34	
	Female	66	66	
2	**Age group**			
	<30	0	0	
	30-39	1	1	1.000
	40-49	10	13	0.5316
	5059	32	33	0.9013
	60-69	38	38	1.000
	70-79	19	15	0.4927

3	**Co-morbidity**			
	HTN	50	40	0.5373
	Dyslipidemia	41	34	0.6825
	Thyroid	8	8	0.8534
	CAD	3	7	0.1578
	Renal	5	6	0.6491
	Nil	29	29	0.7249
4	**Social habits**			
	Smokers	13	8	0.2752
	Alcoholics	11	12	0.8348
5	**Quality of pain**			
	Pin Pricking	12	18	0.5715
	Itching	5	8	0.6284
	Cramping	11	6	0.1050
	Burning	10	16	0.4937
	Numbness	64	64	0.2693
	Aching Pain	42	63	0.2898
6	**Distribution**			0.0499
	Upper extremities	16	31	
	Lower extremities	100	95	

Table 2: Socio demographic characteristics of study population

SL No:	Parameters	PG+MC		GP+MC		P value
		Mean	SD	mean	SD	
1	**Duration**					
	DM	12.86	11.5	11.61	7.81	0.3696
	DN	3.09	2.78	3.10	2.54	0.9788
2	**Blood sugar level**					
	FBS	145.03	59.77	145.27	53.88	0.9762
	PPBS	209.26	82.83	199.83	79.41	0.4122
3	**Age**	61.9	9.517452	59.25	9.201494	

Table 3: NPS score of study population

Sl No:	NPS Items	Therapy	Base line mean(SD)	End point mean(SD)	Mean change(SD)	P value
1	Pain Intensity	PG+MC	4.9(2.17)	2.48(2.60)	2.42(2.31)	0.0571
		GP+MC	5.35(1.70)	3.58(2.96)	1.77(2.49)	
2	Sharp Pain	PG+MC	0.95(2.13)	0.63(1.66)	0.32(1.40)	0.7962
		GP+MC	1.09(2.26)	0.83(1.91)	0.26(1.85)	
3	Hot Pain	PG+MC	0.96(2.00)	0.35(1.25)	0.61(1.72)	0.0460
		GP+MC	1.43(2.94)	1.24(2.85)	0.19(1.19)	
4	Dull Pain	PG+MC	2.95(1.94)	1.42(1.98)	1.53(1.70)	0.8831
		GP+MC	3.84(2.06)	2.35(2.43)	1.49(2.12)	
5	Cold Pain	PG+MC	4.51(3.31)	1.8(2.87)	2.72(3.10)	0.0011
		GP+MC	4.24(3.40)	2.89(3.58)	1.35(2.76)	
6	Sensitive Pain	PG+MC	0.03(0.22)	0.01(0.10)	0.02(0.24)	0.2019

		GP+MC	0.1(0.71)	0.12(0.74)	-0.02(0.20)	
7	Itchy Pain	PG+MC	0.64(1.76)	0.32(1.23)	0.32(1.37)	0.5957
		GP+MC	1.05(2.46)	0.83(2.19)	0.22(1.29)	
8	Pain	PG+MC	4.16(2.08)	1.97(2.39)	2.19(2.23)	0.0406
	Unpleasantness	GP+MC	4.69(1.84)	3.13(2.80)	1.56(2.09)	
9	Deep Pain	PG+MC	0.84(1.49)	0.68(1.28)	0.16(1.21)	0.0406
		GP+MC	1.06(1.74)	0.85(1.56)	0.21(1.35)	
10	Surface Pain	PG+MC	5.15(2.26)	2.62(2.77)	2.53(2.41)	0.0131
		GP+MC	5.43(1.87)	3.76(3.18)	1.67(2.45)	

Table 4: NPS mean score at different time interval

Different time interval	Mean (SD)		P value
	PG+MC	GP+MC	
B	2.51(1.62)	2.83(1.96)	0.2097
F1	1.91(1.42)	2.27(1.49)	0.0818
F2	1.30(0.94)	1.97(1.27)	<0.0001
F3	1.22(0.90)	1.96(1.26)	<0.0001

Table 5: Mean change of NPS score

	Mean change (SD)		P value
	PG+MC	GP+MC	
B-F1	0.60(0.51)	0.56(0.48)	0.5686
B-F2	1.21(1.00)	0.86(0.70)	0.0046
B-F3	1.28(1.05)	0.87(0.71)	0.0014

Table 6: Mean score of Rand 36 Health domains of study population

Sl No:	Health Domains	Therapy	Base line mean(SD)	End point mean(SD)	Mean change(SD)	P value
1	PF	PG+MC	45.55(19.36)	57.25(29.08)	11.7(31.32)	0.2312
		GP+MC	48.60(19.78)	55.65(31.52)	7.05(22.76)	
2	RP	PG+MC	69.06(19.59)	73.31(27.01)	4.25(26.43)	0.5976
		GP+MC	69.38(19.21)	71.81(30.93)	2.44(21.76)	
3	BP	PG+MC	47.99(17.09)	63.75(30.92)	15.76(31.19)	0.6033
		GP+MC	47.63(15.08)	61.25(33.94)	13.62(26.78)	
4	GH	PG+MC	50.62(22.74)	51.52(22.02)	0.9(10.49)	0.1641
		GP+MC	51.8(24.20)	54.72(25.23)	2.92(9.96)	
5	VT	PG+MC	50.25(17)	58.81(29.65)	8.56(29.73)	0.9513
		GP+MC	52.88(16.33)	61.19(32.54)	8.31(28.10)	
6	SF	PG+MC	70.(19.04)	73(27.02)	3(27.39)	0.7932
		GP+MC	71.5(18.63)	73.52(29.77)	2.03(24.80)	
7	RE	PG+MC	86.5(13.48)	81.45(24.49)	-5.08(25.47)	0.5436
		GP+MC	87.08(14.06)	83.88(22.52)	-3.2(17.50)	
8	MH	PG+MC	75.1(11.85)	79.15()18.67)	4.05(19.48)	0.4674
		GP+MC	76.1(10.29)	82.1(20.89)	6(18.38)	

Table 7: Adverse drug reactions of the study population

ADR	No of cases (n)	
	PG+MC	GP+MC
Dizziness	6	4
Somnolence	7	3
Fatigue	0	1
Head ache	1	1
Decreased appetite	1	2
Weight gain	1	3
Diarrhoea	0	1
Edema	2	0

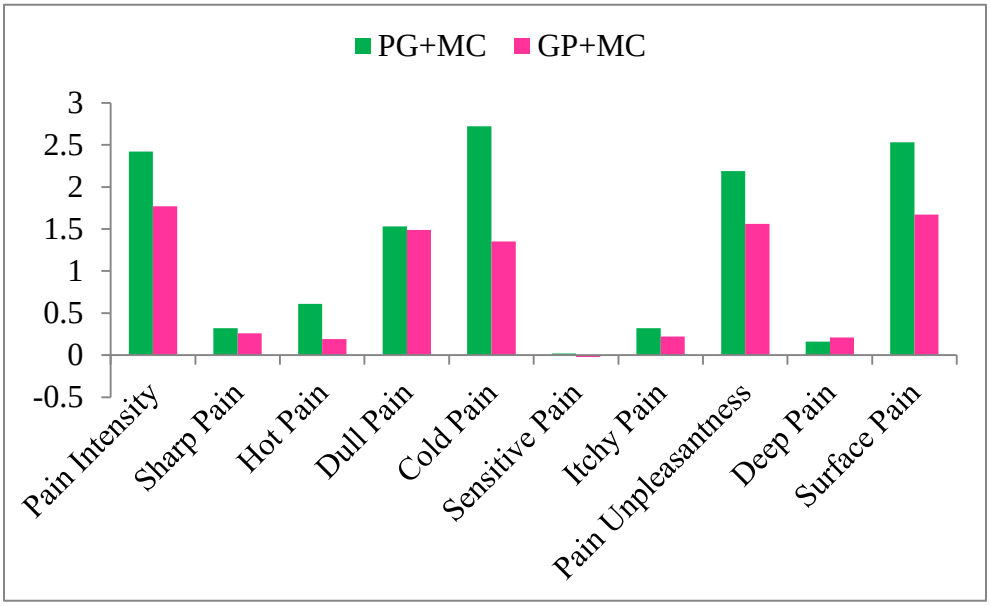

Figure 1: Mean change of NPS score of study population

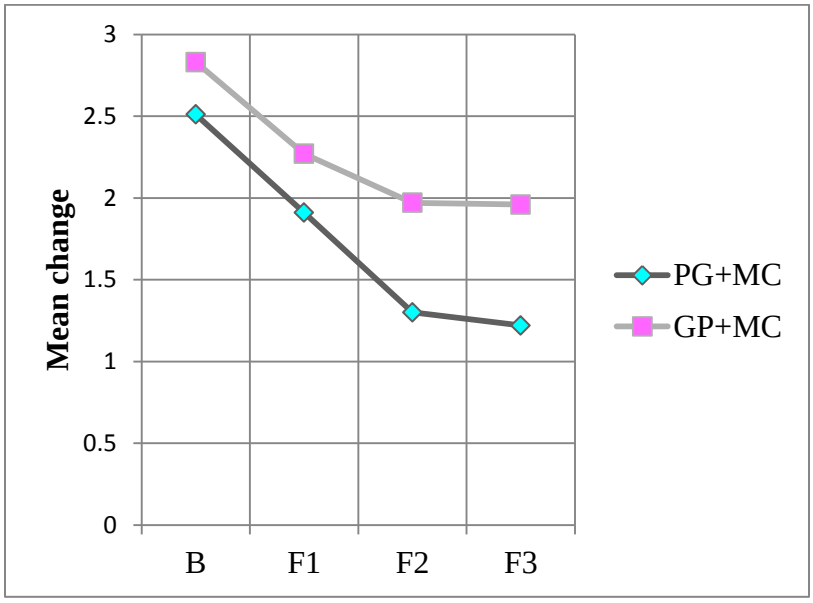

Figure 2: Mean value of NPS score from baseline and each follow-up

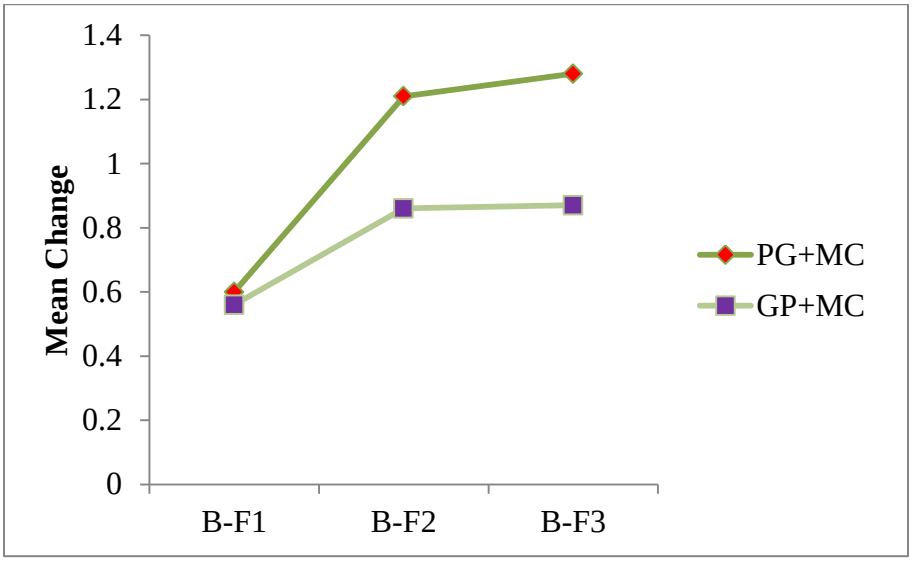

Figure 3: Mean change of NPS score from baseline to each follow-up.

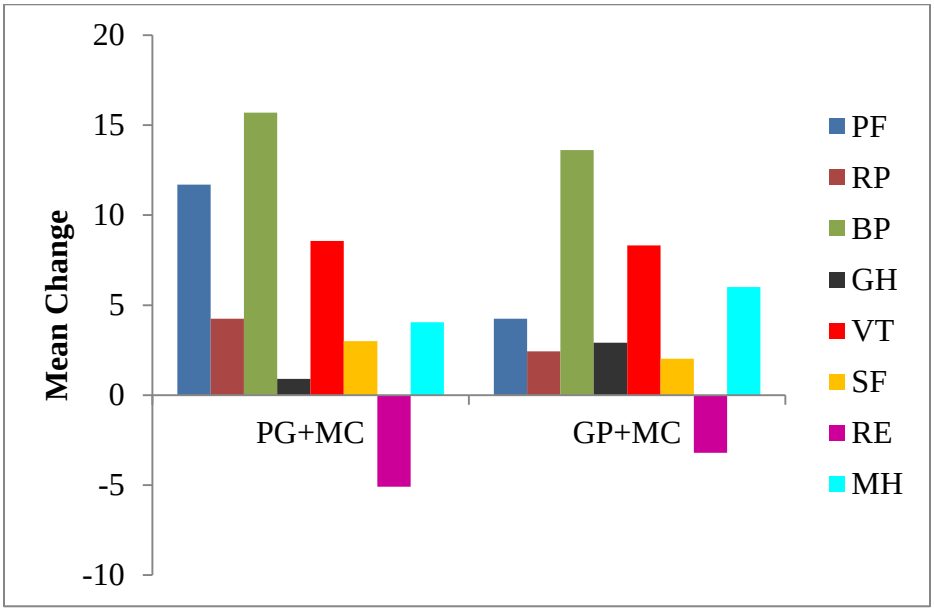

Figure 4: Mean change of health domains of RAND36

CONCLUSION

Both the therapy appears to be significantly efficacious for the treatment of pain and exhibits positive effects on QoL. NPS scores supported the superiority of the pregabalin-methylcobalamin therapy in reducing pain. When each groups were analyzed, there was a significant difference ($p<0.5$) between the pregabalin-methylcobalamin and gabapentin-methylcobalamin groups in mean pain score. Although the difference in quality of life is not significant among both groups, measures relating to physical function, role limitations caused by physical health problems, bodily pain, vitality & social functioning all showed the combination of pregabalin-methylcobalamin to be superior to the combination of gabapentin-

methylcobalamin therapy. Gabapentin-methylcobalamin combination therapy shows an improvement in Quality of Life for three health domains i.e., general health, role limitations caused by emotional problems & mental health. The deviation in mental health, emotional well being and general health may be due to the adverse reactions of the therapy. Clearly, optimal pain reduction in subjects with painful Diabetic Neuropathy has broad therapeutic value because of the strong association of pain with multiple facets of subject function and Quality of Life.

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