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A Prospective Study On The Impact Of Pregabalin Use On The Cognition Of Patients With Neuropathic Pain

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ABSTRACT:

Introduction:

Pregabalin is a newly approved anti-epileptic drug used as an add-on therapy for partial onset seizures and neuropathic pain. Usage of Pregabalin can be associated with various neurotoxic side effects including cognitive impairment.

Aim:

To study the impact of pregabalin use on the cognitive function of patients with neuropathic pain.

Materials and Methods:

The study was conducted on 120 subjects, who were administered pregabalin, over a period of 1 year using the Montreal Cognitive Assessment Scale (MoCA).

Results:

The study was conducted to assess the cognition of patients on Pregabalin for neuropathic pain. Out of the 120 patients involved, the types of neuropathic pain found were as follows: 74 patients (61.66%) had diabetic neuropathy, 16 people (13.33%) had Central Post-Stroke pain, and 12 patient (10%) had Disc prolapsed. The mean overall cognitive score was found to be 21.24 ± 4.39. The mean visuo-spatial score was 3 ± 1.54, naming score was 2.46 ± 0.69, attention score was 3.97 ± 1.38, language score was 2.37 ± 0.8, abstraction score was 1.91 ± 0.31, delayed recall was 2.04 ± 1.33 and orientation was 4.95 ± 1.21.

Conclusion:

Pregabalin were found to cause cognitive impairment and the magnitude of the impact was based on the duration of therapy and dose of the drug.

KEYWORDS: Pregabalin, Cognition, Neuropathic Pain, Analgesic, Anti-Epileptic Drug.

INTRODUCTION:

The term peripheral neuropathy is usually used to describe symmetric and universal damage to adjacent nerves. The damage and clinical manifestations are usually located distally with a proximal progression[1]. Neuropathic pain is distinctly different from nociceptive pain and hence remains the treatment. Antidepressants with both norepinephrine and serotonin reuptake inhibition remain the first line drugs of choice for treatment of neuropathic pain[2]. In addition, the Calcium Channel α_2-δ Ligands Gabapentin and Pregabalin are also used in neuropathic pain. Gabapentin and pregabalin each bind to voltage-gated calcium channels at the α_2-δ subunit and inhibit neurotransmitter release[3]. They have shown efficacy vs placebo in several conditions. Although gabapentin and pregabalin have few drug interactions, both can produce dose-dependent dizziness and sedation, which can be reduced by starting with lower dosages and titrating cautiously[4]. Both medications also require dosage reduction in patients with renal insufficiency, and dosage adjustments can be made in relation to creatinine clearance. Inspite of its potential benefits in neuropathic pain, pregabalin has been reported to have mild negative effects on cognition[5]. A double blind placebo controlled study on cognitive effects of pregabalin, as an anti-epileptic drug, in healthy volunteers found that, at conventional doses and titration, pregabalin induced mild negative cognitive effects and neurotoxicity complaints in healthy volunteers[6]. Another study on the cognitive effects of pregabalin showed that4% of patients taking pregabalin reported cognitive problems[7]. The Pregabalin –

preliminary experience in intractable childhood epilepsy trial reported that 74% of the children exhibited pregabalin-associated cognitive deficits[8]. However, no study has been done to assess the effect of pregablin on cognition when indicated for neuropathic pain. Hence this study was designed to assess the cognitive effects of pregabalin on patients with neuropathic pain.

MATERIALS AND METHODS:

The study was performed at AVS Clinic, Chennai. Ethics approval from Institutional Ethics Committee was obtained prior to the study. Patients of both genders, aged more than 18 years, who were prescribed pregabalin for more than four months, were selected for the study. Patient history was collected and those with a history of dementia, psychiatric disorders were excluded. Pregnant and breast-feeding women were excluded from the study as well. The patients were explained about the study and the consent was obtained. All queries about the study were answered. The patient information was collected and noted in a proforma. The cognition of the patients was assessed using the Montreal Cognitive Scale and the results were noted down and one point was added in case the years of education of the patient was less than 12.

STATISTICAL ANALYSIS:

All the values were expressed as mean ± standard error of mean (SEM). All the groups were compared and tested using logistic linear regression and one way ANOVA using Statistical Package for the Social Science (SPSS) vs 22.0. Values of $P<0.05$ were considered significant.

RESULTS AND DISCUSSION:

The study was conducted to assess the cognition of patients on Pregabalin for neuropathic pain. Out of 120 patients who were assessed, 70 were females and 50 were males. The age of the patients varied from 38 to 71 years. The mean age for females involved in the study was found to be 57.95 ± 7.29 years while the mean age in males was found to be 58.08 ± 7.35 years. Out of the 120 patients involved, the types of neuropathic pain found were as follows: 74 people (61.66%) had diabetic neuropathy, 16 people (13.33%) had Central Post-Stroke pain, 12 people (10%) had Disc prolapse, 5 people (4.1%) had trigeminal neuralgia, 3 people (2.5%) had Spinal cord injury and 3 (2.5%) had entrapment neuropathy, 2 people (1.6%) had alcoholic polyneuropathy and brachial plexitis, hypothyroidism and post-traumatic neuralgia in 1 (0.83%).

The mean overall cognitive score was found to be 21.24 ± 4.39. The mean visuo-spatial score was 3 ± 1.54, naming score was 2.46 ± 0.69, attention score was 3.97 ± 1.38, language score was 2.37 ± 0.8, abstraction score was 1.91 ± 0.31, delayed recall was 2.04 ± 1.33 and orientation was 4.95 ± 1.21.

The predictors of cognitive score were found to be years of education, duration, mean daily dose, sex and smoking, with years of education being the most important predictor, followed by duration for which the drug was consumed, further followed by mean daily dose, sex and smoking (table I for predictors and table II for their significance).

Pregabalin is a newly approved anti-epileptic drug used as an add-on therapy for partial onset seizures and neuropathic pain. Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and anti-seizure effects in animal models[9].

A Japanese study reported that compared to young people, elderly people are more likely to develop cognitive impairments associated with medications. Dementia and delirium (acute confusional state) are known to be associated with drug toxicity and early diagnosis and withdrawal of the offending agent is essential for treating drug-induced dementia and delirium[10].This present study also found that most elders refused to perform visuospatial/ executive activities with respect to MoCA.

Another study which was performed to detect cognitive and psychomotor decrements as well as subject neurotoxicity, in a group of healthy 16 volunteers after 12 weeks of exposure to Pregabalin[11] reported that several tests used to assess neurocognitive performance was impaired in the Pregabalin group. In concordance with that study, duration of pregabalin therapy (as shown in table I and II) was found to be a significant predictor of cognitive impairment, as depicted by the total score of Montreal Cognitive Assessment Scale. Decreased respiration rate occurred in both 75- and 150-mg pregabalin dosing conditions[12] but No evidence and reports of ADRs during the conduction of this study. Guilherme Coco Beltramini et al., (2015)[13] performed a study on the effect of various anti- epileptics on the cognitive functional magnetic resonance imaging. They studied 21 patients with refractory TLE, compared to 20 healthy controls. They used a memory retrieval task paradigm for fMRI and observed an inverse relation between PGB serum level and size of the cluster of activated voxels in mesiotemporal lobes of TLE, possibly associated to reduced cerebral glucose metabolism. There is also a strong evidence of amnesia and memory related problems established with the usage of pregabalin. With chronic usage and high doses, "tip of the tongue" moments and impaired short term memory (eg. Walking into a room and forgetting what you were supposed to do there) are common. Total blackouts do not seem to occur except in combination with other drugs. The association between smoking and cognitive impairment is already well established. In men, 10-year cognitive decline in all tests except vocabulary among never smokers ranged from a quarter to a third of the baseline standard deviation.[14]Faster cognitive decline was observed among current smokers compared to never smokers in men [mean difference in 10-year decline in global cognition=−0.09 (95%CI: −0.15; −0.03) and executive function=−0.11 (−0.17;−0.05)]. Recent ex-smokers had greater decline in executive function (−0.08 (−0.14; −0.02)) while the decline in long-term ex-smokers was similar to that among never smokers. In analyses that additionally took drop-out and death into account, these differences were 1.2 to 1.5 times larger. In women, cognitive decline did not vary as a function of smoking status.[15]

CONCLUSION

This study concludes that there is a definite correlation between the use of pregabalin and decrease in cognitive parameters. Duration and mean daily doses of pregabalin seemed to affect the individual cognitive parameters and hence, the overall scores. This proves that, pregabalin seems to alter cognitive parameters not only in epileptic doses but even in lower doses used for neuropathic pain (75mg – 300mg) which seems to directly affect acute memory and factors related to memory recall ability. This could be of primary concern in geriatric patients with a genetic history of early onset Alzheimer's or with a long-term diabetes mellitus, who are more susceptible to any minute shift in cognitive function[16]. In those cases, an alternate choice of drug (acting on the ongoing C-input to decrease synaptic transmission) could be preferred[17], if the neuropathic pain is severe and the duration of treatment is lengthy or unknown.

This has been the only study to evaluate the usage of pregabalin for doses used in various forms of neuropathic pain. The study has not only found out individual predictors for cognitive impairment during the usage of pregabalin but also acted as a model to further evaluate cognitive scores when years of education, sex, smoking history, duration and dose of the drug is provided. Individual cognitive parameters could not be used as dependent variables and correlated with other cofactors as this study did not include the factors that could affect the same. Hence, it could be further extended to a larger cohort, considering other co-factors that could affect visuo-spacial/ executive, abstract memory, language, attention, memory recall and orientation for increased precision.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

REFERENCES:

1. Hendazhary, Muhammad u. farooq, Minalbhanushali, Arshad majid, Peripheral Neuropathy: Differential Diagnosis and Management *Am Fam Physician.* 2010 Apr 1;81(7):887-892.
2. Sindrup SH1, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain.Basic ClinPharmacolToxicol.2005 Jun;96(6):399-409.
3. Michael A. Rogawski1 and Charles P. Taylor2 Calcium Channel α2–δ Subunit, A New Antiepileptic Drug Target Epilepsy Res. 2006 Jun; 69(3): 183–272.
4. Robert H. Dworkin, PhD, Alec B. O'Connor, MD, Joseph Audette, MD, Ralf Baron, Dr Med, Geoffrey K. Gourlay, PhD, Maija L. Haanpää, MD, PhD, Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update, Mayo Clin Proc. 2010 Mar; 85(3 Suppl): S3-S14.
5. Clair Haslam1 and Turo Nurmikko2, Pharmacological treatment of neuropathic pain in older persons, ClinInterv Aging. 2008 Mar; 3(1): 111–120.
6. Salinsky M, Storzbach D, Munoz S.Cognitive effects of pregabalin in healthy volunteers: a double-blind, placebo-controlled trial,Neurology, 2010 Mar 2;74(9):755-61.
7. Clare. M, Eddy Hughes H (2011), The cognitive impact of antiepileptic drugs, Therapeutic Advances Neurological Disorders. 2011 Nov; 4(6): 385–407.
8. Jan MM, Juberi SA, (2009), Pregabalin : Preliminary experience in retractable childhood epilepsy, Paediatric Neurology, 2009 May;40(5):347-50.
9. http://www.drugbank.ca/drugs/DB00230.
10. Shinohara M, Yamada M, (2012), Drug Induced Cognitive impairment, Brain Nerve, 2012 Dec;64(12):1405-10.
11. Salinsky M, Storzbach D, Munoz S.Cognitive effects of pregabalin in healthy volunteers: a double-blind, placebo-controlled trial,Neurology, 2010 Mar 2;74(9):755-61.
12. Zacny JP, Payce JA, (2012), Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers, Pharmacological and Biochemical Behaviour. 2012 Jan;100(3):560-5.
13. Guilherme Coco Beltramini, Fernando Cendes, and Clarissa Lin Yasuda, The effects of antiepileptic drugs on cognitive functional magnetic resonance imaging, Quant Imaging Med Surg. 2015 Apr; 5(2): 238–246.
14. http://labeling.pfizer.com/ShowLabeling.aspx?id=561.
15. Sabia S1, Elbaz A, Dugravot A, Head J, Shipley M, Hagger-Johnson G, Kivimaki M, [16] Singh-Manoux A., Impact of smoking on cognitive decline in early old age: the Whitehall II cohort study, Arch Gen Psychiatry. 2012 Jun;69(6):627-35. doi: 10.1001/archgenpsychiatry.2011.2016. (last para of discussion)
16. Suzanne M. de la Monte and Jack R. Wands, Alzheimer's Disease Is Type 3 Diabetes–Evidence Reviewed, J Diabetes Sci Technol. 2008 Nov; 2(6): 1101–1113.
17. Alban Latremoliere and Clifford J. Woolf, Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity, J Pain. 2009 Sep; 10(9): 895–926.

TABLES:

Table I

Model Summary

a) Predictors: (Constant), EDUCATION
b) Predictors: (Constant), EDUCATION, DURATION
c) Predictors: (Constant), EDUCATION, DURATION, MEAN DAILY DOSE
d) Predictors: (Constant), EDUCATION, DURATION, MEAN DAILY DOSE, SEX

Table II

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.397[a]	.158	.150	4.065
2	.514[b]	.264	.251	3.816
3	.566[c]	.321	.303	3.682
4	.610[d]	.372	.350	3.557
5	.654[e]	.427	.402	3.411

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	15.963	1.180		13.529	.000
	EDUCATION	.605	.129	.397	4.698	.000
2	(Constant)	19.102	1.345		14.205	.000
	EDUCATION	.578	.121	.379	4.775	.000
	DURATION	-.245	.060	-.327	-4.115	.000
3	(Constant)	22.431	1.682		13.335	.000

ANOVA[f]

	Total	2314.925	119			
2	Regression	611.285	2	305.643	20.990	.000[b]
	Residual	1703.640	117	14.561		
	Total	2314.925	119			
3	Regression	742.413	3	247.471	18.255	.000[c]
	Residual	1572.512	116	13.556		
	Total	2314.925	119			
4	Regression	860.257	4	215.064	17.002	.000[d]
	Residual	1454.668	115	12.649		
	Total	2314.925	119			
5	Regression	988.710	5	197.742	16.998	.000[e]
	Residual	1326.215	114	11.633		
	Total	2314.925	119			

a) Predictors: (Constant), EDUCATION
b) Predictors: (Constant), EDUCATION, DURATION
c) Predictors: (Constant), EDUCATION, DURATION, MEAN DAILY DOSE
d) Predictors: (Constant), EDUCATION, DURATION, MEAN DAILY DOSE, SEX
e) Predictors: (Constant), EDUCATION, DURATION, MEAN DAILY DOSE, SEX, SMOKING
f) Dependent Variable: SCORE

	EDUCATION	.607	.117	.398	5.181	.000
	DURATION	-.246	.057	-.328	-4.280	.000
	MEAN DAILY DOSE	-.027	.009	-.239	-3.110	.002
4	(Constant)	22.427	1.625		13.802	.000
	EDUCATION	.588	.113	.386	5.188	.000
	DURATION	-.285	.057	-.380	-5.003	.000
	MEAN DAILY DOSE	-.029	.008	-.254	-3.419	.001
	SEX	2.069	.678	.232	3.052	.003
5	(Constant)	23.014	1.568		14.675	.000
	EDUCATION	.578	.109	.379	5.316	.000
	DURATION	-.305	.055	-.407	-5.552	.000
	MEAN DAILY DOSE	-.031	.008	-.274	-3.824	.000
	SEX	3.571	.792	.401	4.510	.000
	SMOKING	-3.260	.981	-.287	-3.323	.001

Table III a. Dependent Variable: SCORE