"To evaluate Efficacy and Safety for Management of Neuropathic Pain with Gabapentin, Pregabalin and Amitriptyline"

Dr Nitin Kumar Singh[1], Dr Himanshu Jain[2], Dr Manisha Upadhyay[3], Dr Archana Singh[4]
[1]Assistant Professor, Department of Orthopaedics, GMC AZAMGARH
[2]Assistant Professor, Department of Orthopaedics, MM. Institute of Medical Sciences & Research, Mullana
[3]Professor, Department of Anatomy, GMC AZAMGARH
[4]Associate Professor, Dental College Azamgarh
Corresponding Author: Dr Archana Singh, Associate Professor, Dental College Azamgarh

ABSTRACT

Background: Neuropathic pain caused by a lesion or disease of the somatosensory system. The somatosensory system allows for the perception of touch, pressure, pain, temperature, position, movement and vibration. Gabapentin is an anticonvulsive medication that originally saw use as a muscle relaxer and anti-spasmodic medication. It is also useful in certain types of neural pain control. Pregabalin (PGB) is a newer generation gabapentinoid which followed the use of gabapentin (GBP). This was secondary to limited efficacy in epilepsy as an adjuvant adjuvant antiepileptic drug, but also because of a series of case reports describing the benefits of gabapentin in the treatment of neuropathic pain (NeP). Amitriptyline is FDA approved medication to treat depression in adults. The Non-FDA approved indications are anxiety, post-traumatic stress disorder, insomnia, chronic pain (diabetic neuropathy, fibromyalgia).

Methods: This is a Prospective, comparative, descriptive, three arm study carried out in the Department of Orthopaedics at Tertiary Care Teaching Hospital over a period of 1 year. A total of 210 patients diagnosed with cases of chronic lumbar radiculopathy based on symptoms, clinical examination, X-ray and MRI scan of lumbosacral spine, were randomized into three groups to receive Group A patients received Gabapentine 300 mg, Group B patients received Pregabaline 75 mg, Group C patients received Amitriptyline 10 mg. Patients with either sex with age group of more than 18 years. Diagnosed cases of neuropathic pain due to diabetic peripheral neuropathy, low back pain, post herpetic neuroglia, fibromyalgia and spinal cord injury were included.

Results: At baseline, the Mean±SD of NPRS score in Group A was 7.84±1.53 in Group B and Group C were 7.96 ± 1.62 and 7.73 ± 1.32 respectively and p-value of 0.543 which was not statistically significant. At 15 days, the Mean±SD of NPRS score in Group A was 5.92 ± 1.42, in Group B and Group C were 5.23±1.32 and 6.13±1.43 respectively and p-value of 0.059 which was not statistically significant. At 30 days, the Mean±SD of NPRS score in Group A was 3.91 ± 0.44, in Group B and Group C were 3.33 ± 0.42 and 4.25±0.53 respectively and p-value of 0.001 which was statistically significant.

Conclusions: In patients with NeP Thus, in conclusion three groups Gabapentine, Pregabaline and Amitriptyline are equally efficacious in relieving pain in NeP. Pregabalin has the advantages in terms of Numeric pain rating scale (NPRS) score over the Gabapentine and Amitriptyline. Gabapentine has fewer reported adverse effects and hence a better patient compliance on long term use.

Keywords: Amitriptyline, Pregabalin, Gabapentine, Neuropathic pain

DOI Number: 10.14704/nq.2022.20.9.NQ44336 **Neuro Quantology 2022; 20(9):2891-2896**

Introduction:

Neuropathic pain is usually caused by chronic, progressive nerve disease, and it can also occur as the result of injury or infection. It can flare up at any time without an obvious pain-inducing event or factor. [1] Acute neuropathic pain, while uncommon, can occur as well. Typically, non-neuropathic pain (nociceptive pain) is due to an injury or illness. With neuropathic pain, the pain isn't typically triggered by an event or injury. Instead, the body just sends pain signals to brain unprompted. [2]

Neuropathic pain caused by a lesion or disease of the somatosensory system. The somatosensory system allows for the perception of touch, pressure, pain, temperature, position, movement and vibration. [3] The somatosensory nerves arise in the skin, muscles, joints and fascia and include thermoreceptors, mechanoreceptors, chemoreceptors, pruriceptors and nociceptors that send signals to the spinal cord and eventually to the brain for further processing; most sensory processes involve a thalamic nucleus receiving a sensory signal that is then directed to the cerebral cortex. [4] Lesions or diseases of the somatosensory nervous system can lead to altered and disordered transmission of sensory signals into the spinal cord and the brain; common conditions associated with neuropathic pain include postherpetic neuralgia, trigeminal neuralgia, painful radiculopathy, diabetic neuropathy, amputation, peripheral nerve injury pain and stroke. [5]

Gabapentin is an anticonvulsive medication that originally saw use as a muscle relaxer and anti-spasmodic medication, but later it was discovered it had the potential of the medication as anticonvulsive medication and as an adjunct to more potent anticonvulsants. It is also useful in certain types of neural pain control. [6] It also has an off-label use for neuropathic pain, fibromyalgia, bipolar disorder, postmenopausal hot flashes, essential tremors, anxiety, resistant depressant and mood disorders, irritable bowel syndrome (IBS), alcohol withdrawal, postoperative analgesia, nausea and vomiting, migraine prophylaxis, headache, interstitial cystitis, painful diabetic neuropathy, social phobia, generalized tonic-clonic seizures, pruritus (itching), insomnia, post-traumatic stress disorder (PTSD), and refractory chronic cough. [7]

Pregabalin (PGB) is a newer generation gabapentinoid which followed the use of gabapentin (GBP). This was secondary to limited efficacy in epilepsy as an adjuvant adjuvant antiepileptic drug, but also because of a series of case reports describing the benefits of gabapentin in the treatment of neuropathic pain (NeP). [8] Instead, nearly all of PGB's use is for treatment of NeP, for which PGB was more directly targeted than with gabapentin. In addition, PGB is used frequently in the treatment of anxiety. Although the mechanism of action has not been completely revealed, one known mechanism of action likely contributes to PGB's efficacy, even though other potential mechanisms may also occur. [9]

Amitriptyline is FDA approved medication to treat depression in adults. The Non-FDA approved indications are anxiety, post-traumatic stress disorder, insomnia, chronic pain (diabetic neuropathy, fibromyalgia), irritable bowel syndrome, interstitial cystitis (bladder pain syndrome), migraine prophylaxis, postherpetic neuralgia, and sialorrhea. [10] Amitriptyline is in the tricyclic antidepressant (TCA) drug classification and acts by blocking the reuptake of both serotonin and norepinephrine neurotransmitters. [11]

Material and Methods:

This is a Prospective, comparative, descriptive, three arm study carried out in the Department of Orthopaedics at Tertiary Care Teaching Hospital over a period of 1 year After approval from Institutional Ethics Committee for Medical Research study was initiated.

Inclusion criteria: - Patients with either sex with age group of more than 18 years. Diagnosed cases of neuropathic pain due to diabetic peripheral neuropathy, low back pain, post herpetic neuroglia, fibromyalgia and spinal cord injury.

Exclusion criteria: Patients with history of liver diseases, cardiac illness, renal disease, diabetes, tuberculosis. Pregnant and lactating women. Patients who are immunocompromised. Patients with known hypersensitivity to the study drugs.

Study Design: Total 210 patients were diagnosed neuropathic pain and were randomized into 3 groups.
Group A patients received Gabapentine 300 mg
Group B patients received Pregabalin 75 mg
Group C patients received Amitriptyline 10 mg

Efficacy assessment
Pain assessment was done using numeric pain rating scale (NPRS) at the start of the study (0 day), at 15 days and at 30 days.

ADR Reporting: -
Adverse drug reaction reported by the patient or observed by the clinician during the study was reported using ADR reporting form.

Statistical Analysis: -
Data was entered into MS EXCEL 2017. Data was analyzed using IBM SPSS 25.0 software. Descriptive statistics like frequency, percentage were used to define the variables.

Results:
In each group total 70 patients were there. In Group A: 42 (60 %) were males and 28 (40 %) were females. In Group B: 39 were males (55.7 %) and 31 (44.28 %) were females. In Group C: 41 were males (58.5 %) and 29 (41.42 %)were females.

Table 1: Distribution of patients according to Gender

Gender	Group A	Group B	Group C
Male	42 (60 %)	39 (55.7 %)	41 (58.5 %)
Female	28 (40 %)	31 (44.28 %)	29 (41.42 %)
Total	70 (100 %)	70 (100%)	70 (100%)

Table 2: Distribution of Patients according to Age group

Age-group	Group A	Group B	Group C
18-40	16	14	11
41-60	23	27	26
>61	31	29	33
Total	70 (100 %)	70 (100 %)	70 (100 %)
Mean SD	56.32 ± 4.63	55.23 ± 5.75	55.52± 5.66
F-value	0.242		
p-value	0.516^{ns}		

In Group A: Mean age of patients was 54.38 ± 6.38 years. In group B: Mean age of patients 53.24 ± 6.48 years. In group C: Mean age of patients was 54.48 ± 6.33. The F-value was 0.242 and p-value 0.516 which was statistically not significant.

Table 3: Clinical Diagnosis of the patients

Clinical Diagnosis	Group A	Group B	Group C
Peripheral neuropathy	29	32	30
Diabetic peripheral neuropathy	14	16	14
Trigeminal neuralgia	9	8	9
Central pain after stroke	7	6	8
Post herpetic neuralgia	3	3	2
Myelopathy pain	2	1	2
Central neurogenic pain	2	2	1
Reflex sympathetic dystrophy	1	1	2
Others	3	1	2

Table 4: Comparison of Numeric pain rating scale (NPRS) score in all three groups at baseline after 15 days and after 30 days (ANOVA).

	Baseline Mean±SD	After 15 days Mean±SD	After 30 days Mean±SD
Group A	7.84 ± 1.53	5.92 ± 1.42	3.91 ± 0.44
Group B	7.96 ± 1.62	5.23 ± 1.32	3.33 ± 0.42
Group C	7.73 ± 1.32	6.13 ± 1.43	4.25 ± 0.53
p-value	0.543	0.059	0.001

(P<0.05 is statistically significant, S-significant, NS-not significant, NPRS-Numeric Pain Rating Scale)

At baseline, the Mean±SD of NPRS score in Group A was 7.84±1.53 in Group B and Group C were 7.96 ± 1.62 and 7.73 ± 1.32 respectively and p-value of 0.543 which was not statistically significant. At 15 days, the Mean±SD of NPRS score in Group A was 5.92 ± 1.42, in Group B and Group C were 5.23±1.32 and 6.13±1.43 respectively and p-value of 0.059 which was not statistically significant. At 30 days, the Mean±SD of NPRS score in Group A was 3.91 ± 0.44, in Group B and Group C were 3.33 ± 0.42 and 4.25±0.53 respectively and p-value of 0.001 which was statistically significant.

Table 5: Comparison of percent reduction of NPRS (Numeric Pain Rating Scale) score baseline vs after 30 days in all three groups

Group	Mean reduction
Group A at baseline Vs Group A at 30 days	**3.93**
Group B at baseline Vs Group B at 30 days	**4.63**
Group C at baseline Vs Group C at 30 days	**3.48**

Table 7: Adverse drug reaction in patients in all three groups

	Group A		Group B		Group C		p-value
	n	%	n	%	n	%	
Dizziness	9	12.8	17	24.2	2	2.85	0.031
Sedation	17	24.2	23	32.8	7	10.0	0.020
Constipation	0	00	0	00	6	8.5	0.000
Dry mouth	0	00	0	00	7	10.0	0.000

In present study, occurrence of dizziness was significantly more in group B with 17 patients (24.2%) as compared to group A with 9 patients (12.8%) and group C with 2 patients (2.85%), [p=0.031). The sedation occurred in 23 patients of group B (32.8%), which was significantly more than group A i,e, in 17 patients (24.2%) and group C i.e. 7 patients (10.0%), [P=0.020]. The occurrence of constipation was seen in 6 patients of group C (8.5%) which was significantly more than in Group A and B with 0 patients (0%) [p=0.000]. The occurrence of dryness of mouth was significantly more in group C with 7 patients (10.00%) as compared to that of Group A and B with 0 patients (0%) [p=0.000].

Discussion

In our study, at baseline, the Mean±SD of NPRS score in Group A was 7.84±1.53 in Group B and Group C were 7.96 ± 1.62 and 7.73 ± 1.32 respectively and p-value of 0.543 which was not statistically significant. At 15 days, the Mean±SD of NPRS score in Group A was 5.92 ± 1.42, in Group B and Group C were 5.23±1.32 and 6.13±1.43 respectively and p-value of 0.059 which was not statistically significant. At 30 days, the Mean±SD of NPRS score in Group A was 3.91 ± 0.44, in Group B and Group C were 3.33 ± 0.42 and 4.25±0.53 respectively and p-value of 0.001 which was statistically significant.

The exact mechanism of action with the GABA receptors is unknown; however, that gabapentin freely passes the blood-brain barrier and acts on

neurotransmitters. Gabapentin has a cyclohexyl group to the structure of neurotransmitter GABA as a chemical structure. [12] Even though it has a similar structure to GABA, it does not bind to GABA receptors and does not influence the synthesis or uptake of GABA. Gabapentin works by showing a high affinity for binding sites throughout the brain correspondent to the presence of the voltage-gated calcium channels, especially alpha-2-delta-1, which seems to inhibit the release of excitatory neurotransmitters in the presynaptic area which participate in epileptogenesis. [13] Even though there is no evidence for direct action at the serotonin, dopamine, benzodiazepine, or histamine receptors, research has shown gabapentin to increase total-blood levels of serotonin in healthy control subjects. [14]

Pregabaline is structurally related to the inhibitory neurotransmitter γ-aminobutyric acid (GABA), just as with v. [15] In addition to its impact on the $\alpha_2\delta1$ subunit, there are suggestions that Pregabaline may also modulate GABA concentrations and the glutamate synthesizing enzyme, branched-chain amino acid transaminase (cytosolic form). [16] Gabapentin may also modulate glutamate synthesis indirectly and increase nonsynaptic GABA responses at the GABA-A or GABA-B receptors. In addition, PGB may enhance activity of the neuronal glutamate transporter type 3, increasing glutamatergic responses. When studied in animal analgesic models, gabapentinoids modulate both hyperalgesia (exaggerated response to a painful stimulus) and allodynia (pain-related behavior in response to a normally innocuous stimulus). [17]

Amitriptyline is in the tricyclic antidepressant (TCA) drug classification and acts by blocking the reuptake of both serotonin and norepinephrine neurotransmitters. The three-ring central structure, along with a side chain, is the basic structure of tricyclic antidepressants. Amitriptyline is a tertiary amine with strong binding affinities for alpha-adrenergic, histamine (H1), and muscarinic (M1) receptors. [18] Chronic treatment with amitriptyline desensitizes presynaptic autoreceptors and heteroreceptors, producing long-lasting changes in monoaminergic neurotransmission. [19] It is more sedating and has increased anticholinergic properties compared to other TCAs. Like other antidepressants, the onset of therapeutic action typically begins at approximately 2 to 4 weeks. There have been comprehensive studies of brain-derived neurotrophic factor (BDNF), a major neurotrophic factor that plays an essential role in the formation and survival of neurons during development and synaptic plasticity. [20] The neurotrophic hypothesis of depression suggests that stress-related alterations in BDNF levels occur in key limbic structures to contribute to the pathogenic processes in major depressive disorder(MDD). Chronic treatment with antidepressants increases the BDNF levels, which improves the symptoms associated with MDD. [21]

Conclusion:

Thus, in conclusion three groups Gabapentine, Pregabaline and Amitriptyline are equally efficacious in relieving pain in NeP. Pregabalin has the advantages in terms of Numeric pain rating scale (NPRS) score over the Gabapentine and Amitriptyline. Gabapentine has fewer reported adverse effects and hence a better patient compliance on long term use. Amitriptyline is more cost effective than pregabalin which is an important factor to keep in mind while treating patients.

References:

1. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J Pharmacol. 2007 Jul;151(6):737-48.
2. Hamon M, Blier P. Monoamine neurocircuitry in depression and strategies for new treatments. Prog Neuropsychopharmacol Biol Psychiatry. 2013 Aug 01;45:54-63.
3. Levy MJF, Boulle F, Steinbusch HW, van den Hove DLA, Kenis G, Lanfumey L. Neurotrophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression. Psychopharmacology (Berl). 2018 Aug;235(8):2195-2220.
4. Venkatakrishnan K, Schmider J, Harmatz JS, Ehrenberg BL, von Moltke LL, Graf JA, Mertzanis P, Corbett KE, Rodriguez MC, Shader RI, Greenblatt DJ. Relative contribution of CYP3A to amitriptyline clearance in humans: in vitro and in vivo

studies. J Clin Pharmacol. 2001 Oct;41(10):1043-54.
5. Deisenhammer EA, Whitworth AB, Geretsegger C, Kurzthaler I, Gritsch S, Miller CH, Fleischhacker WW, Stuppäck CH. Intravenous versus oral administration of amitriptyline in patients with major depression. J Clin Psychopharmacol. 2000 Aug;20(4):417-22.
6. Leucht C, Huhn M, Leucht S. Amitriptyline versus placebo for major depressive disorder. Cochrane Database Syst Rev. 2012 Dec 12;12:CD009138.
7. Uguz F. A New Safety Scoring System for the Use of Psychotropic Drugs During Lactation. 2021 Jan-Feb 01Am J Ther. 28(1):e118-e126.
8. Nagler EV, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). Nephrol Dial Transplant. 2012 Oct;27(10):3736-45.
9. Güloglu C, Orak M, Ustündag M, Altunci YA. Analysis of amitriptyline overdose in emergency medicine. Emerg Med J. 2011 Apr;28(4):296-9.
10. Zechnich R. Delirium and tricyclic antidepressants. Am J Psychiatry. 1984 Dec;141(12):1642-3.
11. Nishimura T, Maruguchi H, Nakao A, Nakayama S. Unusual complications from amitriptyline intoxication. BMJ Case Rep. 2017 Oct 10;2017
12. Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry. 2014 Apr;171(4):404-15.
13. Rabenda V, Nicolet D, Beaudart C, Bruyère O, Reginster JY. Relationship between use of antidepressants and risk of fractures: a meta-analysis. Osteoporos Int. 2013 Jan;24(1):121-37.
14. Fornaro M, Anastasia A, Valchera A, Carano A, Orsolini L, Vellante F, Rapini G, Olivieri L, Di Natale S, Perna G, Martinotti G, Di Giannantonio M, De Berardis D. The FDA "Black Box" Warning on Antidepressant Suicide Risk in Young Adults: More Harm Than Benefits? Front Psychiatry. 2019;10:294.
15. Kiyan S, Aksay E, Yanturali S, Atilla R, Ersel M. Acute myocardial infarction associated with amitriptyline overdose. Basic Clin Pharmacol Toxicol. 2006 May;98(5):462-6.
16. Sabah KMN, Chowdhury AW, Islam MS, Saha BP, Kabir SR, Kawser S. Amitriptyline-induced ventricular tachycardia: a case report. BMC Res Notes. 2017 Jul 14;10(1):286.
17. Michalets EL, Williams CR. Drug interactions with cisapride: clinical implications. Clin Pharmacokinet. 2000 Jul;39(1):49-75.
18. Dougherty JA, Young H, Shafi T. Serotonin syndrome induced by amitriptyline, meperidine, and venlafaxine. Ann Pharmacother. 2002 Oct;36(10):1647-8.
19. Unterecker S, Pfuhlmann B, Kopf J, Kittel-Schneider S, Reif A, Deckert J. Increase of Heart Rate and QTc by Amitriptyline, But Not by Venlafaxine, Is Correlated to Serum Concentration. J Clin Psychopharmacol. 2015 Aug;35(4):460-3.
20. Lynch R. Tricyclic antidepressant overdose. Emerg Med J. 2002 Nov;19(6):596.
21. Ramasubbu B, James D, Scurr A, Sandilands EA. Serum alkalinisation is the cornerstone of treatment for amitriptyline poisoning. BMJ Case Rep. 2016 Apr 11;2016:10.1136/bcr-2016-214685