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COMPARATIVE EVALUATION OF ANALGESIC ACTIVITY OF SSRI (FLUOXETINE) AND SNRI (DULOXETINE AND VENLAFAXINE) IN EXPERIMENTALLY INDUCED CHRONIC NEUROPATHIC PAIN MODEL

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Keywords:

Antidepressants, Chronic pain, Neuropathic pain, Spared-nerve injury, Von frey filament

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ABSTRACT: Objectives: To investigate and compare the analgesic effect of fluoxetine (FLU), duloxetine (DUL) and venlafaxine (VEN) in animal models of chronic pain. **Methods:** Chronic pain was induced in albino rats using spared nerve injury and vincristine. Rats were divided into Control group/ Normal Saline (NS5), DUL group, FLU group, and VEN group. In spared nerve injury, sural branch of sciatic nerve was kept intact while another two branches, common peroneal and tibial nerve ligated and cut. In the vincristine-induced neuropathic pain model, vincristine was administered along with test drugs for 5 days and then 2 days gap and then for 5 days. Mechanical allodynia and hyperalgesia developed in animals were indicative of pain. Pain assessment was done by using von frey filaments by measuring paw withdrawal threshold (PWT) on day 7 in spared nerve injury and on 7 and 14 days of vincristine administration. **Results:** In spared nerve injury, DUL and FLU showed a significant increase in PWT compared to the control group. Venlafaxine had no analgesic action in spared nerve injury model of neuropathic pain. DUL and FLU showed significant reversal of mechanical allodynia. There was no difference between the analgesic activity of fluoxetine and venlafaxine. DUL significantly reverses the development of mechanical allodynia as compared to fluoxetine and venlafaxine. **Conclusion:** Duloxetine was more effective as an analgesic than fluoxetine and venlafaxine in neuropathic pain.

INTRODUCTION: According to India State-Level Disease Burden Initiative Mental Disorder Collaborators, the prevalence of depression in India is 3.1-3.6 % affecting 45.7 billion populations in 2017 with prevalence slightly higher in females as compared to males [1].

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Chronic persistent pain is associated greater prevalence of psychiatric comorbidity than the general population and depression is one of the co-morbidities associated with chronic pain [2].

There is increased co-occurrence between chronic pain and depression. There is a strong link between them. The relationship is bidirectional, with 20-50 % of patients with chronic pain suffering from depression [3]. Depression often goes unnoticed in patients with chronic pain. Thus because of associated conditions, patients with chronic pain with depression may experience more pain than chronic pain patients without depression [2] and in

patients with chronic pain, depression is often unnoticed and left untreated [3]. Depression and chronic pain are closely related in occurrence, development, and mechanism. Depression is a result of decreased level of monoamine neurotransmitter (5-HT/serotonin, norepinephrine) in the brain and decreased level of brain-derived neurotrophic factors, which also regulate hypersensitivity to pain by increasing the expression of protein kinase C. Apart from this, inflammatory factors and increased glutamate receptor activity also responsible for depression and pain [4]. Modulation of pain signal is mediated by descending inhibiting pain pathway consisting of 5-HT/serotonin, norepinephrine, and dopamine. If the activity of these neurotransmitters decreases in descending inhibitory pain pathway, it contributes to chronic pain [5]. The same neurotransmitter is also involved in the development of depression. Thus, targeting this shared mechanism can treat both conditions simultaneously when these are present simultaneously.

Chronic pain lasts> 3 months or more and is divided into primary and secondary pain syndrome. Neuropathic pain is a pain that is caused by lesion or disease of the somatosensory nervous system and is characterized by the development of allodynia and hyperalgesia [6]. About 15-25 % of chronic pain is neuropathic and includes diabetic neuropathy pain, post-herpetic neuralgia, and radiculopathy. Non-steroidal anti-inflammatory drugs are mainly used for non-neuropathic pain, while opioids are the mainstay for acute pain and not considered for the treatment of chronic pain because of the risk of misuse, abuse, and addiction [7]. Antidepressants are first-line agents for the treatment of neuropathic pain by their effects on the improvement of depressive state even in a non-depressed patient while taking less time to decrease chronic pain than depression. Tricyclic antidepressants (TCAs; amitriptyline, nortriptyline) serotonin-norepinephrine reuptake inhibitors (SNRIs; duloxetine and venlafaxine) are used for the management of chronic neuropathic pain by virtue of their mechanism of inhibition of the reuptake of monoamines in descending modulatory system [8]. SSRIs block the reuptake of serotonin and increase serotonin levels in the synaptic cleft, enhancing neurotransmission [10].

Apart from inhibiting the reuptake of serotonin and norepinephrine, TCA also binds to histaminergic, cholinergic, and adrenergic receptors and contributes to their side effects [5, 8, 9]. Efficacy of SSRIs like fluoxetine is lower than TCAs and SNRIs while SNRIs lacking side effects of TCAs [5].

Duloxetine is US-FDA approved for the management of chronic pain conditions diabetic peripheral neuropathy and fibromyalgia as well as chronic musculoskeletal pain and stress urinary incontinence in both men and women while lacking muscarinic, cholinergic, alpha 2-adrenergic and H1 histaminergic receptors side effect [11]. Venlafaxine is being used off label for fibromyalgia, diabetic neuropathy, and lack cholinergic and histaminergic side effect like duloxetine [12]. Antidepressants that inhibit reuptake of both noradrenaline and serotonin has stronger analgesic effect than a drug that inhibit reuptake of only one neurotransmitter and noradrenaline plays greater role than serotonin in analgesic action [13]. Some reviews and research suggested that fluoxetine is ineffective in chronic pain [10]. Thus, because of conflicting results about fluoxetine (SSRIs), approved use of duloxetine (SNRIs) in chronic pain but not that of venlafaxine, this study is undertaken to evaluate and compare analgesic effect of fluoxetine, duloxetine and venlafaxine in chronic pain model in albino rats.

MATERIAL AND METHODS: The study was conducted after approval of the Institutional Animal Ethics Committee with approved number GMC/IEAC/120/2018 and according to CPCSEA guidelines from April-2019 to March-2020.

Animals: Healthy albino Wistar rats of either sex weighing 150 to 250 grams were used for the experiment. Animals were housed in central animal houses and maintained on a standard diet (rat pellet) and water ad libitum. Animals were maintained at 23 ± 1^0C, with enough humidity, and on 12-hour light-dark cycle. Animals were purchased from LACSMI Biofarms Pvt Ltd, Pune.

Drugs and Chemicals: Duloxetine and venlafaxine were purchased from TCI Chemicals, Chennai. Fluoxetine was purchased from Rajesh Chemicals, Mumbai. All drugs were of analytical grade. All drugs were dissolved in normal saline with a sufficient quantity of solvent.

Fresh solutions of the drug were prepared before each experiment. The chemicals used were isoflurane as an anesthetic obtained from TCI chemicals Chennai. Vincristine was obtained from Pro Lab Marketing Pvt. Ltd, Delhi. All the drugs were given intraperitoneally.

Grouping of Animals: Rats were grouped as below with 6 rats in each group for the experiment. Total 54 rats were used for the experiment. During consecutive experiments, a washout period was given depending upon nature of the drug. Rats were tagged for identification during each experiment to avoid mixing of animals between two groups.

Groups Abbreviation:

Control-Normal saline 5 mg/kg: NS5

Duloxetine 10 mg/kg: DUL10

Duloxetine 30 mg/kg: DUL30

Fluoxetine 5 mg/kg: FLU5

Fluoxetine 10 mg/kg: FLU10

Fluoxetine 15 mg/kg: FLU15

Venlafaxine 10 mg/kg: VEN10

Venlafaxine 22.5 mg/kg: VEN22.5

Venlafaxine 50 mg/kg: VEN50

Methods: For the evaluation of chronic pain, two neuropathic pain models were used. One was the peripheral nerve injury model (spared nerve injury model) and the drug-induced neuropathic pain model (vincristine-induced neuropathic pain).

Spared Nerve Injury Model of Neuropathic Pain: Spared nerve injury model of neuropathic pain described in an article by Guida *et al*. focuses on spared nerve injury model described by Decosterd and Woolf [14]. In this model of neuropathic pain, two of three branches of the sciatic nerve, namely the tibial and a common peroneal nerve, cut distal from sciatic trifurcation, leaving the third nerve (sural nerve) intact. This results in hyperalgesia and allodynia in the sural nerve territory and does not involve any inflammation at the injury site. Rats were anesthetized with isoflurane using an induction box. Anesthesia was maintained using cotton soaked in isoflurane placed in a tube near rat snout. Hairs on the left thigh were shaved, and the rat was placed in the lateral position on their right side. The paw was elevated and stretched perpendicular to the body. The area was cleaned using betadine and isopropyl alcohol. After palpation of the trochanter and iliac crest, an incision was made on the imaginary line between these points, and toward the toes and skin on the lateral surface of the thigh was incised with scalpel blade. An incision was made through bicep femoris. Retraction was maintained using forceps.

After identifying three branches of sciatic nerve, the tip of micro forceps was placed beneath the common peroneal and tibial nerve, and the nerve was tightly ligated using suture 3-0. After ligation, nerves were cut distal to ligation using micro scissors. Care was taken to avoid contact with the sural nerve. Then muscle was sutured using suture material using needle holder. The skin was closed using ethilon 3-0 suture material. After surgery and completion of anesthesia, the rat was placed in a cage. Because of the uninjured sural nerve, hyperalgesia and allodynia development in the sural nerve territory, which was analyzed using von frey filament. Allodynia was measured on day 7 after the administration of drugs. Before administering a drug, baseline response to von frey filament was taken. Von frey filaments were applied in sural nerve territory (applied over lateral one-third of paw) in increasing order, and response to von frey filament was measured at 30, 60, 90, 120, and 180 minutes after drug administration on day 7.

Vincristine Induced Neuropathic Pain: Vincristine is an anti-neoplastic agent used to treat leukemias, lymphoma, and sarcomas. Peripheral neuropathy/neuropathic pain is the most common side effect of this anticancer drug causing paresthesia, allodynia, and hyperalgesia. Before administration of vincristine, the rat was weighed, and vincristine was injected intraperitoneally in a dose of 100 µg/kg daily at the same time, along with daily administration of test drugs. Doses were given for consecutive 5 days and then 2 days gap and then for 5 days [15]. After treatment, maximum allodynia and hyperalgesia developed in 14 days, measured by von frey filament.

Paw withdrawal threshold was measured by von frey filament on day 1 of vincristine administration before the drug given and then day 7 and day 14 and compared to that of day 1.

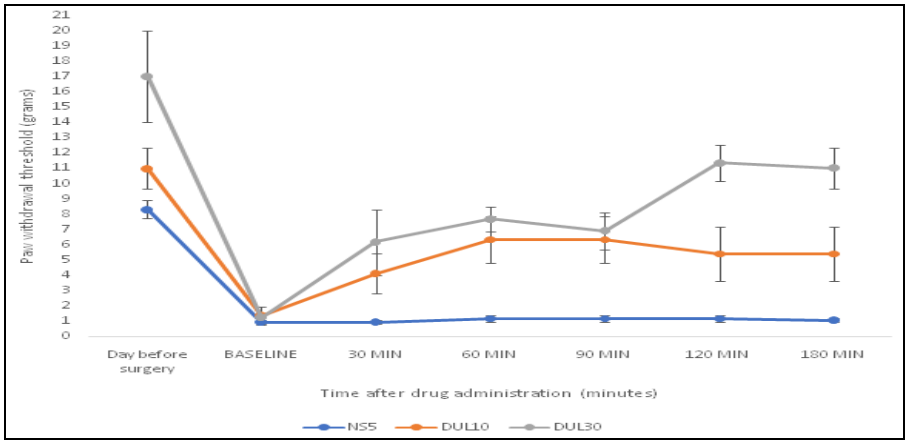
Von Frey Filament Testing: Von frey testing method was introduced in 1950s to measure sensory threshold in humans by applying perpendicular force through calibrated filament with known force at which they bend and measuring threshold.

Von frey filament testing was used to measure mechanical allodynia in an animal model by using a simplified up and down method as described by Chaplan et al. The Von frey filament is a set of 20 nylon filaments with increasing forces from 0.oo8 to 300 grams. Filament from numbers 7 through 14 is used to analyze mechanical allodynia in rat [16]. Rats were placed in an acrylic chamber suspended above the wire grid and allowed to acclimate for 1 h. When rats were relaxed, von frey filaments were pressed perpendicular against the sural nerve territory until the filament was slightly buckled and held for 3 seconds. If there was a negative response, the next higher filament was used, and if the response was positive, the next lower filament was used. In this way, the paw withdrawal threshold was measured. A positive response was noted as a sharp withdrawal of paw or licking of paw or flinching after filament application. In the case of spared nerve injury model, an increase in paw withdrawal threshold was denoted as analgesic activity. In contrast, in the vincristine-induced neuropathic pain model, the persistence of basal paw withdrawal threshold or increase in paw withdrawal threshold was taken as analgesic activity.

Statistical Analysis: Results were expressed as Mean ± SEM (Standard Error of Mean). Data were analyzed by one-way ANOVA followed by a post hoc tukey test using SPSS 21.0 software. 'p-value <0.05 was taken as statistically significant.

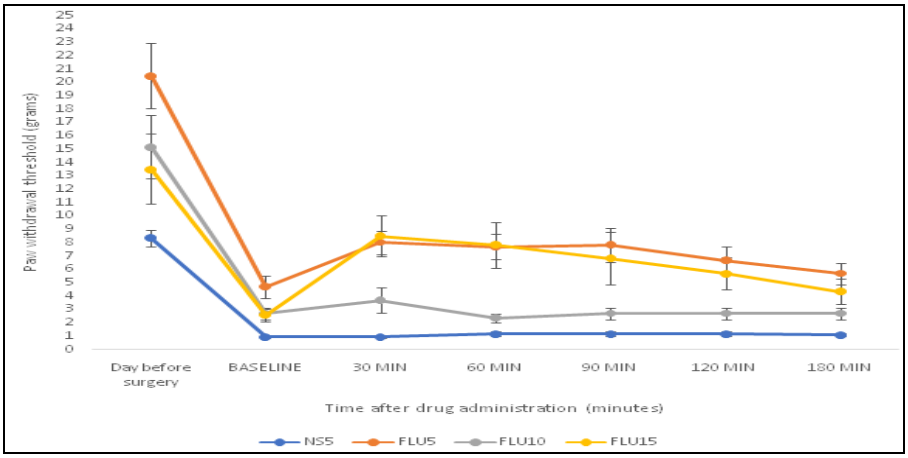
RESULTS:

Effect of Drugs on Paw Withdrawal Threshold in Spared Nerve Injury Model of Neuropathic Pain: NS5 did not increase PWT as compared to baseline. On day 7, compared to baseline paw withdrawal threshold (PWT), DUL10 shows a significant increase in PWT with a maximum PWT of 6.33 grams at 60 and 90 minutes after drug administration. DUL30 shows a significant increase in PWT at 60, 90, 120, and 180 min, with a maximum PWT of 11.33 grams at 120 min. FLU5 significantly increases PWT at 30, 60, 90 min after drug administration with a maximum PWT of 8.0 grams at 30 min, while FLU15 shows a significant increase in PWT at 30, 60, 90, and 120 minutes with a maximum PWT of 8.5 grams at 30 min. FLU10 did not increase PWT significantly as compared to baseline. VEN10 increases PWT only at 90 minutes with maximum PWT of 4.23 grams while VEN 22.5 increases PWT at 60, 90, and 120 min with a maximum PWT of 4.17 at 90 and 120 min. VEN50 significantly increases PWT with a maximum PWT of 4.83 grams at 180 minutes. Compared to the normal saline NS5 group, DUL10 showed a significant increase in PWT only at 30 min while DUL30 showed a significant increase in PWT at 60, 90, 120, and 180 min. (See graph 1).

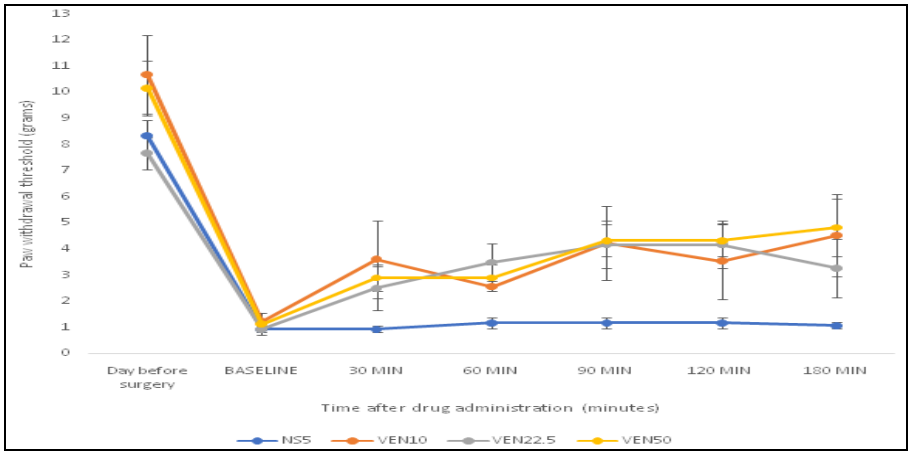


GRAPH 1: EFFECT OF DULOXETINE ON PAW WITHDRAWAL THRESHOLD AS COMPARED TO NORMAL SALINE IN SPAREDNERVE INJURY MODEL OF NEUROPATHIC PAIN (* = P value < 0.05 as compared to control group normal saline and $ = P value > 0.05 as compared to duloxetine 30 mg/kg).

Similarly, FLU5 shows a significant increase in PWT at 30, 60, 90, and 120 minutes, while FLU15 showed a significant increase in PWT at 30, 60, and 90 minutes as compared to normal saline. (See graph 2) Venlafaxine did not show an increase in PWT as compared to normal saline. (See graph 3).



GRAPH 2: EFFECT OF FLUOXETINE ON PAW WITHDRAWAL THRESHOLD AS COMPARED TO NORMAL SALINE IN SPARED NERVE INJURY MODEL OF NEUROPATHIC PAIN. (*= P value < 0.05 as compared to control group normal saline and $ = P value > 0.05 as compared to duloxetine 30 mg/kg).



GRAPH 3: EFFECT OF VENLAFAXINE ON PAW WITHDRAWAL THRESHOLD AS COMPARED TO NORMAL SALINE IN SPARED NERVE INJURY MODEL OF NEUROPATHIC PAIN. (*= P value < 0.05 as compared to control group normal saline and $ = P value > 0.05 as compared to duloxetine 30 mg/kg).

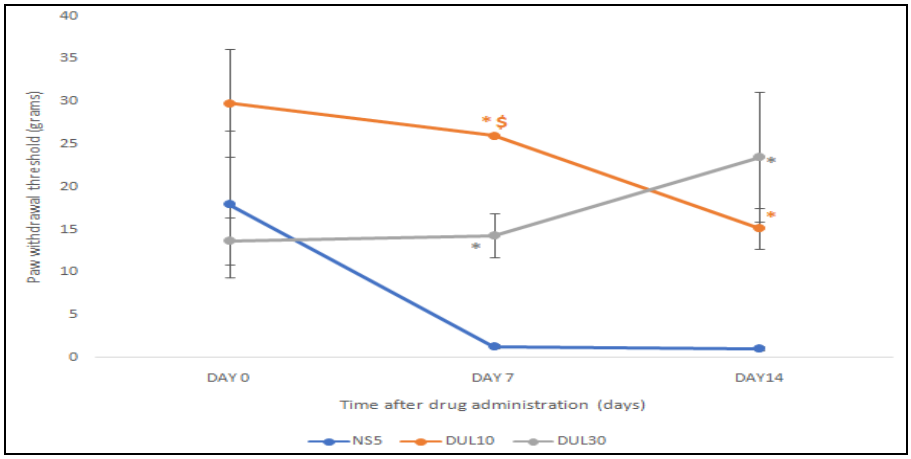
DUL30 significantly increases PWT compared to DUL10, while FLU5 more significantly increases PWT compared to FLU10 and FLU15 at 60 min. Venlafaxine groups (VEN10, VEN22.5, and VEN50) did not show a statistically significant difference in PWT. As compared to FLU5, DUL30 significantly increases PWT.

DUL30 showed a significant increase in PWT as compared to fluoxetine, and venlafaxine at 60 and 180 minutes.

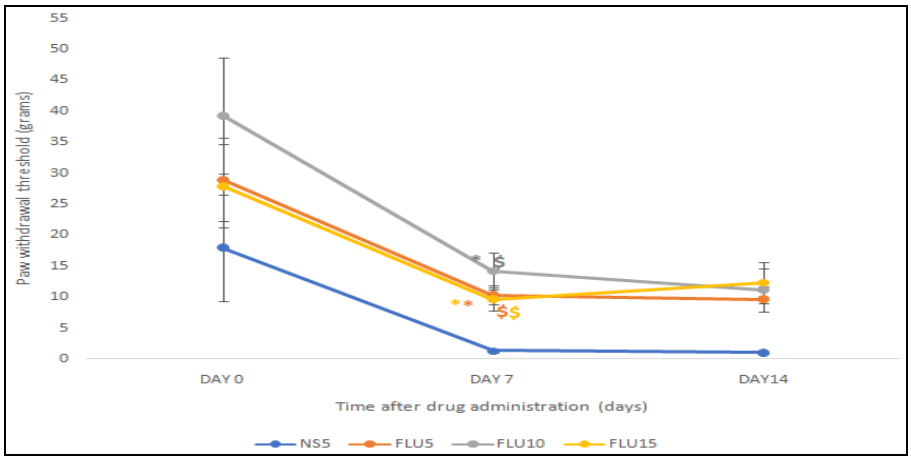
FLU5 and FLU15 more significantly increase PWT at 30 min and 60 min. Thus, as an analgesic, duloxetine 30 mg/kg was more effective than fluoxetine 5 mg/kg and venlafaxine in spared nerve injury model of neuropathic pain.

Effect of Drugs on Paw Withdrawal Threshold in Vincristine Induced Neuropathic Pain Model: Normal saline did not increase paw withdrawal threshold. DUL10 prevents the decrease in paw withdrawal threshold significantly with a paw withdrawal threshold of 26 grams and 15.17 grams on day 7 and day 14, respectively, with day 0 paw withdrawal threshold of 29.83 grams, while DUL30 did not prevent this decrease in paw withdrawal threshold on day 7 and day 14. FLU5 reverses mechanical allodynia on day 14 but not on day 7. FLU10 also reverses the development of mechanical allodynia. VEN10 and VEN22.5 decreased the paw withdrawal threshold significantly and did not prevent the development of mechanical allodynia. FLU15 and VEN50

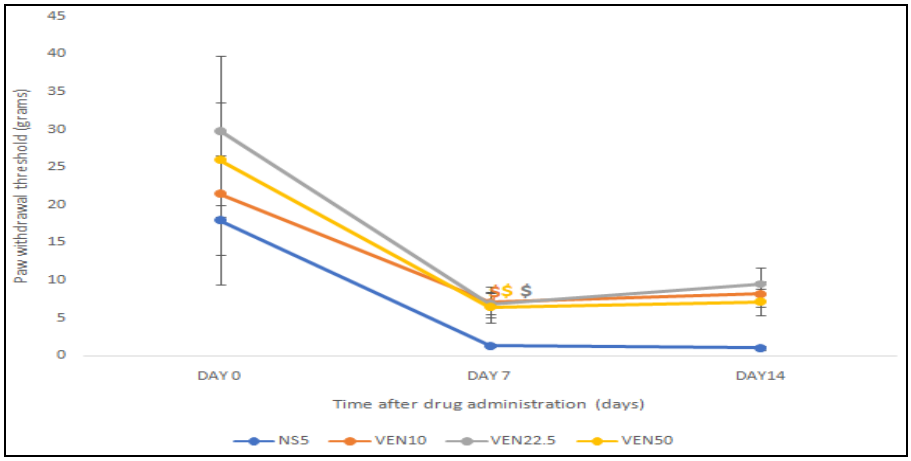
significantly ameliorated mechanical allodynia on day 7 but not on day 14. As compared to normal saline, DUL10, DUL30, FLU5, FLU10, and FLU15 showed significant reversal of mechanical allodynia on day 7, while DUL10 and DUL30 also reversed mechanical allodynia on day 14 also. DUL10 was more effective in reversing the development of mechanical allodynia than DUL30. (See Graphs 4, 5 and 6).



GRAPH 4: EFFECT OF DULOXETINE ON PAW WITHDRAWAL THRESHOLD AS COMPARED TO NORMAL SALINE IN VINCRISTINE INDUCED NEUROPATHIC PAIN. (* = p value <0.05 as compared to normal saline and $ = p value > 0.05 as compared to duloxetine 10 mg/kg).



GRAPH 5: EFFECT OF FLUOXETINE ON PAW WITHDRAWAL THRESHOLD AS COMPARED TO NORMAL SALINE IN VINCRISTINE INDUCED NEUROPATHIC PAIN. (*= P value <0.05 as compared to normal saline and $ = P value > 0.05 as compared to duloxetine 10 mg/kg).



GRAPH 6: EFFECT OF VENLAFAXINE ON PAW WITHDRAWAL THRESHOLD AS COMPARED TO NORMAL SALINE IN VINCRISTINE-INDUCED NEUROPATHIC PAIN. ($ = P-value > 0.05 as compared to duloxetine 10 mg/kg).

There was no difference between the analgesic activity of FLU5, FLU10, and FLU15 as well as between VEN10, VEN22.5, and VEN50. DUL10 significantly prevents the development of mechanical allodynia compared to other groups on day 7 but not on day 14. There was no difference between the analgesic activity of DUL30 and fluoxetine and venlafaxine on day 7, but on day 14, DUL30 ameliorates mechanical allodynia as compared to VEN10 and VEN50. There was no difference between analgesic activity of fluoxetine and venlafaxine. Thus, Duloxetine had a significant effect in reversing mechanical allodynia in vincristine-induced neuropathic pain as compared with fluoxetine and venlafaxine, while fluoxetine and venlafaxine had no effect on paw withdrawal threshold in vincristine induced neuropathic pain.

DISCUSSION: In this study, we evaluated the analgesic effect of fluoxetine, duloxetine, and venlafaxine in chronic pain, especially neuropathic pain using spared nerve injury model and vincristine-induced neuropathic pain model. Spared nerve injury model produces sensory symptoms of hyperalgesia and allodynia develops after 3 days and lasting about 7 months following injury. These sensory symptoms appear in the territory of uninjured sural nerve located on lateral area of paw. Spared nerve injury model induces pain matrix characterized by altered glial homeostasis, neuronal excitability, synaptic plasticity and transmission in spinal and supraspinal areas mimicking clinical neuropathic pain [14].

We used drugs in various doses like duloxetine in 10 and 30 mg/kg, fluoxetine in 5, 10 and 15 mg/kg, and venlafaxine in 10, 22.5 and 50 mg/kg. In this study, duloxetine was effective in both spared nerve injury model and the vincristine-induced neuropathic pain model. It was seen that duloxetine was more effective than fluoxetine and venlafaxine in reversing mechanical allodynia. But in the case of vincristine-induced neuropathic pain, duloxetine did not completely ameliorate mechanical allodynia but prevented the development of mechanical allodynia as compared to the control group, normal saline. Venlafaxine did not show any effect in neuropathic pain in this study, while fluoxetine had an effect in spared nerve injury model but not in vincristine-induced neuropathic pain but the effect is less significant than that of duloxetine.

There have been several reports indicating duloxetine have a beneficial effect in nerve injury and chemotherapy-induced neuropathic pain. In a study conducted by Rodrigues *et al*, duloxetine 30 mg/kg showed analgesic effect in chronic constriction injury of sciatic nerve, a model of neuropathic pain stating that duloxetine exerts secondary downstream mechanism and neuroplasticity changes [17]. In one study, repeated administration of duloxetine reversed increased tactile allodynia caused by oxaliplatin in mice, but single dose of duloxetine was ineffective in reversing tactile allodynia induced by oxaliplatin indicating that duloxetine has anti-hyperalgesic and anti-allodynic effect in chemotherapy-induced neuropathic pain [18] which is consistent with our study.

A study that compares various antidepressants in neuropathic pain model showed that duloxetine suppressed mechanical allodynia while fluoxetine did not suppress mechanical allodynia indicating that central recruitment of descending noradrenergic pathway is important for the nociceptive response while peripheral recruitment of noradrenergic fibers sprouting from dorsal root ganglia after nerve injury responsible for nociceptive action of antidepressant [19]. Apart from this, duloxetine protects against oxaliplatin and paclitaxel induced neurotoxicity and axonal injury and mainly involve NF-κB and P38 MAPK in neuroprotective effect of duloxetine [20].

Rode *et al.* studied the effect of venlafaxine in the spared nerve injury model of neuropathic pain in rats. They showed that venlafaxine upto 50 mg/kg doses did not affect mechanical allodynia, consistent with our finding [21]. While another study evaluated the effects of venlafaxine in a mouse model of oxaliplatin-induced mechanical allodynia and stated that venlafaxine suppresses mechanical allodynia induced by oxaliplatin, and the result of the study also stated that noradrenergic and serotonergic system involved in the venlafaxine induced analgesia. α2 receptors and 5-HT3 receptors are involved in the analgesic action of venlafaxine. Apart from this, venlafaxine at high doses acts as SNRI, while at low doses like SSRI [22, 23]. Lian *et al.,*. Studied the effect of fluoxetine in chronic stress model of neuropathic pain in tail-flick test and by using von frey filament where

fluoxetine shows high tail-flick latency and low withdrawal threshold which is the same finding as in this study [24]. One study analyzed the analgesic effect of fluoxetine, venlafaxine and vortioxetine chronic constriction injury of sciatic nerve in mice. This study showed that fluoxetine did not affect allodynia and paw withdrawal threshold, while venlafaxine and vortioxetine had analgesic action in the neuropathic model [25].

The mechanism by which antidepressants exert their analgesic action mainly involves modulation of pain by increasing the level of monoamines by inhibiting the reuptake of serotonin and noradrenaline. Antidepressants that block serotonin and noradrenaline transporter prevent presynaptic reuptake and increase noradrenaline and serotonin, thus strengthening the descending inhibitory pain pathway.

It is clear from preclinical studies that noradrenaline acting on α2 receptors exerts its analgesic action while serotonin acts on 5-HT_{1A}/5-HT_{1B}/5-HT_{1D}/5-HT_{5A} receptor, exerts its analgesic action. Bravo *et al.,* while focusing on neuropathic pain management, stated that SSRIs are poor in relieving chronic pain and are not used as first-line treatment for neuropathic pain, while duloxetine and venlafaxine have dual action on serotonin and noradrenaline reuptake inhibition are effective in the treatment of neuropathic pain [26].

Apart from that, antidepressants decrease neuropathic pain in patients without depression. Reuptake inhibition if noradrenaline plays a greater role in the analgesic action of antidepressants [27]. It is found that balanced inhibition of serotonin and norepinephrine is more beneficial in relieving pain than inhibition of either one. And thus, duloxetine being a balanced inhibitor, is more useful for the management of chronic pain conditions [28]. Therefore, duloxetine is approved for the treatment of fibromyalgia, diabetic peripheral neuropathy, and musculoskeletal pain and is used off-label to treat peripheral neuropathy secondary to chemotherapy administration and urinary incontinence [11, 29]. In contrast, venlafaxine is used off-label for diabetic neuropathy and peripheral neuropathy secondary to chemotherapy administration but is not approved and is currently evaluated for chronic neuropathic pain [12, 29].

CONCLUSION: In conclusion, the results indicate that duloxetine, in comparison with fluoxetine and venlafaxine, has significant analgesic action and is used to manage chronic pain conditions. Venlafaxine, as compared to approved duloxetine, has less analgesic action and is hence not approved for the management of chronic pain. Fluoxetine has analgesic action but is less compared to duloxetine. Fluoxetine and venlafaxine may need further studies for their use in neuropathic pain because of inconsistent results. Thus, duloxetine but not venlafaxine and fluoxetine are approved for treating chronic pain conditions, while venlafaxine and fluoxetine need further studies in chronic and neuropathic pain conditions.

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REFERENCES:

1. Sagar R, Dandona R, Gururaj G, Dhaliwal RS, Singh A and Ferrari A: The burden of mental disorders across the states of India: The Global Burden of Disease Study 1990–2017. The Lancet Psychiatry 2020; 7(2): 148-61.
2. Lee HJ, Choi EJ, Nahm FS, Yoon IY and Lee PB: Prevalence of unrecognized depression in patients with chronic pain without a history of psychiatric diseases. The Korean Journal of Pain 2018; 31(2): 116-24.
3. Mills SEE, Nicolson KP and Smith BH: Chronic pain: a review of its epidemiology and associated factors in population-based studies. British Journal of Anaesthesia 2019; 123(2): e273-283.
4. Sheng J, Liu S, Wang Y, Cui R and Zhang X: The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plasticity 2017; 2017: 1-10.
5. Kwon M, Altin M, Duenas H and Alev L: The role of descending inhibitory pathways on chronic pain modulation and clinical implications. Pain Practice 2014; 14(7): 656-67.
6. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019; 160(1): 19-27.
7. Cohen S, Vase L and Hooten W: Chronic pain: an update on burden, best practices and new advances. The Lancet 2021; 397(10289): 2082-2097.
8. Patel R and Dickenson AH: Neuropharmacological basis for multimodal analgesia in chronic pain. Postgraduate Medicine 2021; 1-15.
9. Cavalli E, Mammana S, Nicoletti F, Bramanti P and Mazzon E: The neuropathic pain: An overview of the

current treatment and future therapeutic approaches. International Journal of Immunopathology and Pharmacology 2019; 33: 1-10.
10. Urits I, Peck J, Orhurhu MS, Wolf J, Patel R, Orhurhu V, Kaye AD and Viswanath O: Off-label antidepressant use for treatment and management of chronic pain: evolving understanding and comprehensive review. Current Pain and Headache Reports 2019; 23(9): 1-0
11. Dhaliwal JS, Spurling BC, Molla M. Duloxetine. [Updated 2021 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2022 Jan.
12. Singh D and Saadabadi A: Venlafaxine. [Updated 2021 Oct 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535363.
13. Obata H: Analgesic mechanisms of antidepressants for neuropathic pain. International Journal of Molecular Sciences 2017; 18(11): 2483.
14. Guida F, De Gregorio D, Palazzo E, Ricciardi F, Boccella S and Belardo C: Behavioral, biochemical and electrophysiological changes in spared nerve injury model of neuropathic pain. International Journal of Molecular Sciences 2020; 21(9): 3396.
15. Li D, Chung G and Kim SK: The involvement of central noradrenergic pathway in the analgesic effect of bee venom acupuncture on vincristine-induced peripheral neuropathy in rats. Toxins 2020; 12(12): 775.
16. Bonin RP, Bories C and De Koninck Y: A simplified up-down method (SUDO) for measuring mechanical nociception in rodents using von Frey filaments. Molecular Pain 2014; 10: 26.
17. Rodrigues RF, Kawano T, Placido RV, Costa LH, Podestá MHMC and Santos RS: Investigation of the Combination of Pregabalin with Duloxetine or Amitriptyline on the Pharmacokinetics and Antiallodynic Effect During Neuropathic Pain in Rats. Pain Physicia 2021; 24: 511-20.
18. Sałat K, Furgała-Wojas A and Sałat R: The microglial activation inhibitor minocycline, used alone and in combination with duloxetine, attenuates pain caused by oxaliplatin in mice. Molecules 2021; 26(12): 3577.
19. Salvat E, Yalcin I, Muller A and Barrot M: A comparison of early and late treatments on allodynia and its chronification in experimental neuropathic pain. Molecular Pain 2017; 14: 1-10.
20. Meng J, Zhang Q, Yang C, Xiao L, Xue Z and Zhu J: Duloxetine, a balanced serotonin-norepinephrine reuptake inhibitor, improves painful chemotherapy-induced peripheral neuropathy by inhibiting activation of p38 MAPK and NF-κB. Frontiers in Pharmacology 2019; 10: 365.
21. Rode F, Broløs T, Blackburn-Munro G, Bjerrum OJ. Venlafaxine compromises the antinociceptive actions of gabapentin in rat models of neuropathic and persistent pain. Psychopharmacology 2006; 187(3): 364-75.
22. Bravo L, Llorca-Torralba M, Berrocoso E and Micó JA: Monoamines as drug targets in chronic pain: focusing on neuropathic pain. Frontiers in Neuroscience 2019; 1268.
23. Li Y, Lustberg MB and Hu S: Emerging Pharmacological and Non-Pharmacological Therapeutics for Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy. Cancers 2021; 13(4): 766.
24. Lian YN, Chang JL, Lu Q, Wang Y, Zhang Y and Zhang FM: Effects of fluoxetine on changes of pain sensitivity in chronic stress model rats. Neuroscience Letters. 2017; 651: 16-20.
25. Zuena A, Maftei D, Alemà G, Dal Moro F, Lattanzi R and Casolini P: Multimodal antidepressant vortioxetine causes analgesia in a mouse model of chronic neuropathic pain. Molecular Pain 2018; 14: 174480691880898.
26. Bravo L, Llorca-Torralba M, Berrocoso E and Micó JA: Monoamines as drug targets in chronic pain: focusing on neuropathic pain. Frontiers in Neuroscience 2019; 1268.
27. Hayashida K and Obata H: Strategies to treat chronic pain and strengthen impaired descending noradrenergic inhibitory system. International Journal of Molecular Sciences 2019; 20(4): 822.
28. Li Y, Lustberg MB and Hu S: Emerging Pharmacological and Non-Pharmacological Therapeutics for Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy Cancers 2021; 13(4): 766.
29. Fanelli D, Weller G and Liu H: New Serotonin-Norepinephrine Reuptake Inhibitors and Their Anesthetic and Analgesic Considerations. Neurology International 2021; 13(4): 497-509.

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